The effect of modafinil on simulated driving performance

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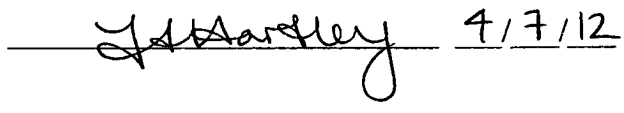
Statement

I declare that this thesis is my own work and that, to the best of my knowledge and belief, it does not contain material from published sources without proper acknowledgement, nor does it contain material which has been accepted for the award of any other higher degree or graduate diploma in any university.



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The effect of modafinil on simulated driving performance

Jessica Hartley

Abstract

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide, Modavigil®) is a novel stimulant medication shown to improve alertness, cognitive performance and subjective mood. It is thought to be a superior alternative to amphetamines; with its neuropsychological profile and resulting behavioural effects suggesting it is functionally distinct from conventional stimulants, such as dexamphetamine. The current study investigated acute driving-related cognitive skills and simulated driving performance following a 200mg single dose of modafinil in well rested individuals, using measures of driving performance that have been demonstrated to be negatively affected by dexamphetamine. Twenty participants completed the double-blinded placebo-controlled crossover study, completing a battery of cognitive tasks (Occupational Safety Performance Assessment Technology, reaction time index, stop signal task, rapid visual information processing) and a simulated driving scenario at baseline and at 3 hours post drug administration (peak drug level). No deleterious effects of modafinil were found, which is in contrast to dexamphetamine use on comparable tasks. Subjective levels of alertness were higher at peak modafinil compared to placebo; modafinil lead to faster stop signal reaction time on the stop signal task; less lateral lane deviation and a trend towards fewer centre line crossings were apparent during simulated driving. The findings of the current study indicated that modafinil selectively improves neuropsychological task performance in a functionally different way compared to conventional stimulants, specifically dexamphetamine. These differences in cognitive and behavioural performance may be attributable to the differing neurochemical profile of these drugs, and demonstrate a reduced risk to road safety for modafinil in comparison to existing stimulant medications.

What is modafinil?

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is a novel stimulant medication shown to improve alertness, cognitive performance and subjective mood. It has been available in Australia since 2002, listed as a Schedule IV prescription drug, for treatment of excessive daytime sleepiness associated with narcolepsy, chronic shift work disorder and obstructive sleep apnoea (MIMS, 2009). However in recent years the majority of modafinil prescriptions have been dispensed 'off label' (the practice of prescribing pharmaceuticals for an unapproved indication) (Ballon & Feifel, 2006) for a range of neuropsychiatric and medical conditions involving fatigue, as well as for healthy people who need to stay alert and awake when sleep deprived, such as physicians on night call (Minzenberg & Carter, 2008). The number of modafinil prescriptions filled in community pharmacies in Australia has risen dramatically over recent years. According to the Department of Health and Aging, it is estimated that 698 modafinil prescriptions were filled in 2003 (Department of Health and Aging, 2005), this increased to 7,734 in 2008 (Department of Health and Aging, 2009); an increase of 1108% over 5 years. Furthermore, only 1822 of the scripts filled in 2008 were PBS subsidised (i.e. prescribed for on label use), this suggests that the remainder of modafinil use was off label (Department of Health and Aging, 2009).

Neurochemical effects of modafinil

Modafinil selectively improves neuropsychological performance (Turner et al., 2003) with marked specificity for sleep and arousal systems in the brain; this is in comparison with other stimulants, such as amphetamines, which have more diffuse targets; primarily increasing dopamine and to a lesser extent norepinephrine activity

(Gurtman, Broadbear, & Redman, 2008). The neuropsychological profile of modafinil suggests that it is functionally distinct from conventional stimulants, specifically dexamphetamine (Solanto, 1998). Whilst the exact mechanism by which modafinil produces wakefulness and cognitive enhancement is still unknown, it is widely accepted that the drug is structurally unrelated to amphetamines and has a differing neurochemical profile and resulting behavioural effects (Minzenberg & Carter, 2008). The key neurotransmitters that are thought to be involved in modafinil actions are norepinephrine, dopamine, glutamate, GABA, histamine and orexin. Modafinil is thought to have a limited liability for abuse, in contrast to amphetamines with little or no drug tolerance evident after weeks of continuous use (Caldwell & Caldwell, 2005). Additionally, doses of up to 600 mg revealed no psychoactive effects in cocaine addicts (Rush, Kelly, Hays, & Wooten, 2002). Abuse liability is strongly reliant on the extent of dopamine activity in the mesolimbic dopamine 'reward' pathway (primarily in the nucleus accumbens) (Di Chiara, Acquas, Tanda, & Cadoni, 1993) which may suggest modafinil actions are specifically different in this pathway when compared to dexamphetamine.

It is widely accepted that modafinil increases extracellular levels of norepinephrine in the prefrontal cortex as well as in the hypothalamus (de Saint Hilaire, Orosco, Rouch, Blanc, & Nicolaidis, 2001). Norepinephrine is one of the key neurotransmitters involved in the arousal system of the brain. The pharmacological action of modafinil increases norepinephrine levels, leading to increased arousal (see Figure 1). Modafinil administration has been demonstrated to enhance the norepinephrine-induced inhibition of sleep promoting neurons in the ventrolateral preoptic nucleus (Gallopin, Luppi, Rambert, Frydman, & Fort, 2004). It is thought that the adrenergic receptor- mediated effects (norepinephrine and epinephrine

receptors) following modafinil administration are likely a result of an increase in norepinephrine, and that norepinephrine mediates modafinil effects on cognition and behaviour (Minzenberg & Carter, 2008).

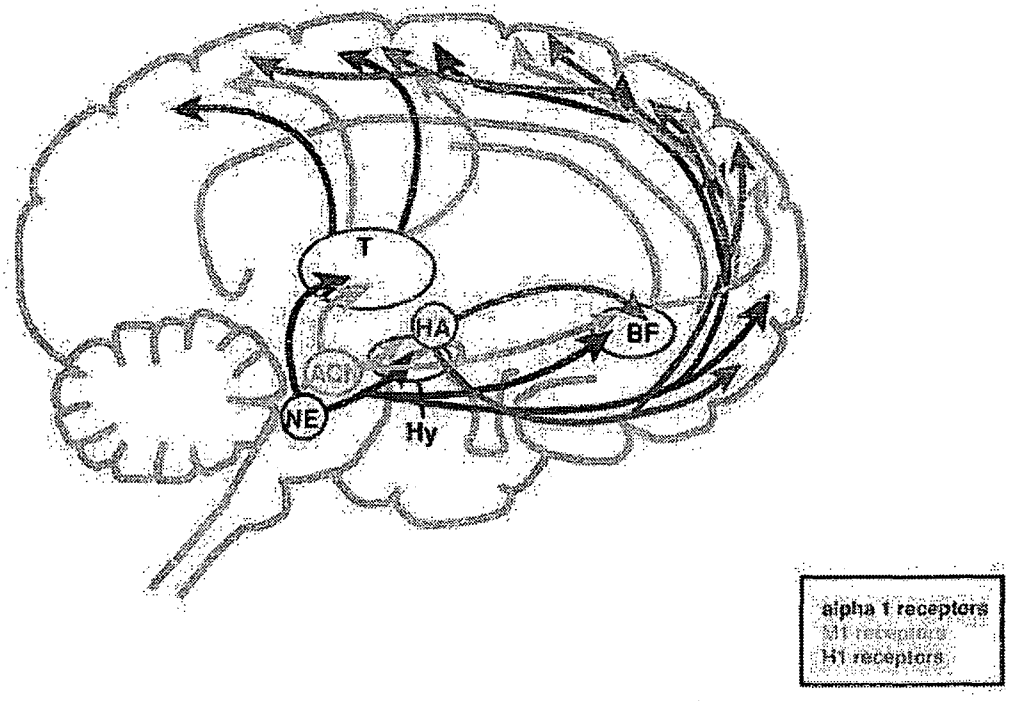

Figure 1. Neurotransmitters of cortical arousal. The neurotransmitters acetylcholine (ACh), histamine (HA), and norepinephrine (NE) are all involved in arousal pathways connecting neurotransmitter centres with the thalamus (T), hypothalamus (Hy), basal forebrain (BF), and cortex. Thus, pharmacological actions at their receptors could influence arousal. Modafinil has been demonstrated to increase NE and HA levels (Stahl, 2011).

There have been mixed findings when it comes to the effect modafinil has on the neurotransmitter dopamine. Early researchers claimed that, unlike amphetamine, modafinil appeared to produce arousal through a mechanism that did not involve dopaminergic activity (Ferraro et al., 1997; Lin et al., 1992; Taylor & Russo, 2000). However a study, using rodents, showed a modest effect of modafinil on binding to the dopamine transporter (DAT) (Mignot, Nishino, Guilleminault, & Dement, 1994). A more recent study was conducted using positron emission tomography (PET) to study the brains of rhesus monkeys. This research group found a significant binding

of the DAT in the striatum and the norepinephrine transporter (NET) in the thalamus after 2, 5 and 8mg/kg of modafinil was administered (Madras et al., 2006). Researchers have also shown that intravenous administration of 128mg/kg of modafinil leads to significantly increased extracellular dopamine levels in the prefrontal cortex of rats (de Saint Hilaire et al., 2001), however it should be noted that this dosage would not be replicated in humans receiving therapeutic levels of the drug, which is typically 200 mg per day (Stahl, 2011). At therapeutic levels Stahl (2011) has shown modafinil has a low affinity for the DAT and questions whether its binding here is relevant to clinical effects. Whilst the research is inconsistent it suggests that the arousal and behavioural effects of modafinil may be least partly mediated by dopamine, and may favour corticostriatal regions of the brain instead of subcortical limbic structures like amphetamine (Minzenberg & Carter, 2008).

More consistently reported are the effects modafinil has on the glutamate and gamma-aminobutyric acid (GABA) neurotransmitter systems. It is thought that the stimulatory effects on glutamate are the result of an interaction with the adrenergic system. This is because norepinephrine assists in the synaptic release of glutamate onto medial prefrontal cortex pyramidal cells. This release of glutamate following modafinil is blocked by prazosin (Marek & Aghajanian, 1999), a blood pressure medication that constricts the action of norepinephrine; demonstrating the role of norepinephrine in glutamate production. Modafinil causes dose-dependent decreases in GABA throughout the brain. This effect appears to be a secondary result of the effect modafinil has on other neurotransmitter systems; primarily the serotonin system (5HT), as pre-treating rats with $5HT_2$ receptor antagonists eliminates modafinil-induced reductions in GABA levels throughout the cortex (Tanganelli, Fuxe, Ferraro, Janson, & Bianchi, 1992) .

Modafinil was originally passed by the Australian Therapeutic Goods Association for the treatment, among other things, of narcolepsy. This condition is characterized by a deficiency of orexin in the brain (Nishino, 2003). Given that modafinil is effective at treating this disorder, it gives reason to suggest it may have relevant effects on this neurochemical system. However, a study in 2005 found that modafinil is more effective in inducing wakefulness in orexin-knockout mice, compared to wild-type mice (Willie et al.). Therefore the arousal effects of modafinil do not seem to be mediated by orexin, with the effect orexin has on the cognitive effects of modafinil remaining unknown.

It is thought modafinil effects on histamine, a key neurotransmitter in facilitating arousal, are also secondary to the effect modafinil has on other neurotransmitter systems. However, a role for histamine has been demonstrated in a range of learning and memory tasks (Passani et al., 2000). Therefore increased histamine activity may also mediate the cognitive effects shown on modafinil.

To summarize, modafinil is a psychostimulant that differs from amphetamines in neurochemical profile and resulting behavioural effects. Currently, the only neurotransmitters that modafinil has been shown to directly bind to are the norepinephrine transporter and to a lesser extent the dopamine transporter, which it inhibits at modest levels in comparison to dexamphetamine. The administration of modafinil subsequently leads to significantly higher extracellular dopamine, norepinephrine, 5HT, glutamate and histamine levels, and decreased levels of GABA; with the effects appearing more prominent in the neocortex compared to subcortical areas. Modafinil effects on norepinephrine (and dopamine) appear to be primary, with the effects on glutamate, GABA, 5HT, orexin and histamine appearing to be secondary.

The effect modafinil has on cognition: is it superior to dexamphetamine?

Modafinil is thought to be a superior alternative to dexamphetamine when it comes to its wake-promoting properties and cognitive enhancing effects. Modafinil appears to enhance cognitive performance in both well-rested adults and sleep-deprived adults; however overall, findings are inconsistent. In healthy humans modafinil has been found to enhance digit span, visual pattern recognition, spatial planning and stop signal reaction time, complemented by a slowing in latency in decision making, spatial planning and delayed matching (Turner et al., 2003). Participants reported feeling more alert, attentive and energetic on the drug (Turner et al). Another study found an improvement in working memory, without a speed-accuracy trade off on attention tasks (Muller, Steffenhagen, Regenthal, & Bublak, 2004). A single dose of 100mg of modafinil has been shown to improve digit span and sustained attention (Randall, Viswanath, et al., 2005), however no significant improvements were found on a range of other cognitive tasks measured by this research group at this dose. The tasks included motor screening, delayed matching to sample (DMS), intra/extra dimensional set shift (ID/ED), stockings of Cambridge (SOC), rapid visual information processing (RVP) (all from the CANTAB), logical memory (WMS-R), the Stroop test, trail making test, controlled oral word association test and clock drawing (Randall, Shneerson, Plaha, & File, 2003) These null findings may, however, be an artefact of the student sample used, reflecting a ceiling effect on performance due to higher than average IQs.

Table 1 demonstrates the results of numerous studies that have examined the cognitive effects of modafinil. Motoric reaction time was examined in well rested participants by Randall, Shneerson and File (2005) and Baranski, Pigeau, Dinich and Jacobs (2004). Randall et al found no effect of modafinil on reaction time index

(simple and choice), with Baranski et al finding it improved four-choice serial reaction time.

Processing speed has been examined by Randall, Shneerson and File (2005) and Muller et al (2004) with no significant findings for well rested individuals on digit cancellation and symbol copying. However, Hart et al (2006) demonstrated an increase in total number of responses made on a digit symbol task following 200mg and 400mg doses of modafinil.

Improvements on more complex cognitive tasks have also been shown after modafinil administration. Stop signal reaction time has been shown to significantly improve after 100mg and 200mg dose of modafinil in well rested individuals demonstrating improved inhibition (Turner et al., 2003). Performance on Trail Making, as a test of executive functioning and cognitive flexibility has been examined with no significant improvements during modafinil compared to placebo in well-rested individuals (Randall, Fleck, Shneerson, & File, 2004; Randall, Shneerson, et al., 2005; Randall et al., 2003).

Wesensten (2005) compared 400 mg modafinil, 20 mg dexamphetamine and 600 mg caffeine on measures of alertness and executive function over a period of 85hours of sleep deprivation. Measures were taken bi-hourly with participants ingesting the allocated drug after being awake for 64 hours (see Table 1 for details of tests administered). The study found that all three drugs were equally effective at reversing sleep loss-induced alertness and psychomotor performance decrements, compared to placebo. However few significant drug effects were found on tasks of executive function. All three drugs improved simple reaction time and performance on the Wisconsin Card Sorting Test (a measure of executive functioning), modafinil and caffeine improved performance on the Biber Cognitive Estimation test (a

measure of estimation skills), with dexamphetamine impairing Stroop performance. These differing and selective improvements give evidence to the drugs differing neurochemical properties but do not provide a clear picture of neuroenhancement.

Table 1
Effects of Modafinil on Cognition and Information Processing

Author	Year	Sample	Dose	Measures	Significant effects	Lack of effect
Well rested participant sample						
Randall et al.	(2005)	Healthy adults	0, 100, 200mg	RTI, RVP,SWM, ID/ED, SOC, symbol copying, digit symbol substitution, digit cancellation, PASAT, trail making, stroop test, clock drawing, COWAT	↓RT stroop-colour naming, ↑accuracy digit sustained attention (200mg), ↑digit span forward & back (100mg)	RTI, RVP, SWM, ID/ED, SOC , symbol copying, digit symbol cancellation, SWM logical memory, PASAT, trail making, COWAT
Baranski, Pigeau, Dinich, & Jacobs	(2004)	Healthy adults	Placebo, 4mg/kg (approx. 300mg)	Serial RT logical reasoning, visual comparison, mental addition and vigilance, confidence judgments	Serial RT, logical reasoning	Addition, line discrimination, confidence judgments
Randall, Fleck, Shneerson, & File	(2004)	Healthy adults	0, 100, 200mg	MOT, DMS, RVP, ID/ED,SOC,logical memory (WMS-R) stroop test, clock drawing, trail making, COWAT	At 200mg:↓RT stroop colour naming, ↑accuracy clock drawing, ↓ accuracy ID/ED	MOT,DMS, RVP, SOC, spatial planning, sustained attention, logical memory, trail making, COWAT
Müller, Steffenhage, Regenthal, & Bublak	(2004)	Healthy adults	0, 200mg	DMS, simple digit maintenance, letter cancellation, trail making	↑accuracy DMS long delay and manipulation	Simple digit maintenance, letter cancellation, trail making

Note: BCET-Biber Cognitive Estimation Test; CANTAB-Cambridge Neuropsychological Test Automated Battery; COWAT-controlled oral word association test; DMS-delayed matching to sample; FIT-fitness impairment test; ID/ED-intra/extra dimensional set shift; MOT-motor screening; NTOL-new tower of London spatial planning task; PAL-paired associates learning; PASAT-paced auditory serial addition task; PRT- pattern recognition memory; PVT-psychomotor vigilance test; RTI-reaction time index: RVP-rapid visual information processing; RT-reaction time; SOC-stocking of Cambridge; SST-stop signal task; SSRT-stop signal reaction time; SWM-spatial working memory; WCST-Wisconsin card sorting task

Table 1. Continued
Effects of Modafinil on Cognition and Information Processing

Author	Year	Sample	Dose	Measures	Significant effects	Lack of effect
Well rested participant sample						
Randall , Shneerson, Plaha & File	(2003)	Healthy adults (high IQ)	0, 100, 200mg	MOT, DMS, ID/ED, SOC, RVP, stroop test, trail making, COWAT, clock drawing, logical memory (WMS-R)	No significant effects	MOT, DMS, ID/ED, SOC, RVP stroop test, trail making, COWAT, clock drawing, logical memory
Turner et al.	(2003)	Healthy adults	0, 100, 200mg	PRT, PAL, DMS, SWM, ID/ED, NTOL, digit span (WAIS), gamble task, SST	↑accuracy digit span, PRM, NTOL, stop signal, ↓RT DMS & SSRT	PAL, SWM,ID/ED, digit span
Sleep deprived participant sample						
Hart et al.	(2006)	Healthy adults in simulated night shift	0, 200, 400mg	Digit recall task, digit symbol substitution task, divided attention task, the rapid information task, repeated acquisition task	At both doses: ↑accuracy on immediate digit recall,↑ accuracy digit symbol, ↑sequence learning, ↑ sustained attention, ↓false alarms on divided attention	n/a
Wesensten, Killgore, & Balkin	(2005)	Sleep deprived healthy adults	400mg (parallel groups)	PVT, PAB battery, stroop test, WCST, COWAT, BCET, FIT, animal fluency	↓simple RT, ↑ accuracy WCST	Stroop, verbal fluency, simple RT and WCST comparable to caffeine 600mg, d-AMP 20mg

Note: BCET-Biber Cognitive Estimation Test; CANTAB-Cambridge Neuropsychological Test Automated Battery; COWAT-controlled oral word association test; DMS-delayed matching to sample; FIT-fitness impairment test; ID/ED-intra/extra dimensional set shift; MOT-motor screening; NTOL-new tower of London spatial planning task; PAL-paired associates learning; PASAT-paced auditory serial addition task; PRT- pattern recognition memory; PVT-psychomotor vigilance test; RTI-reaction time index: RVP-rapid visual information processing; RT-reaction time; SOC-stocking of Cambridge; SST-stop signal task; SSRT-stop signal reaction time; SWM-spatial working memory; WCST-Wisconsin card sorting task

A systematic review by Repantis, Schlattmann, Laisney and Heuser (2010) examined the cognitive, emotional and motivational effects of methylphenidate (Ritalin, a psychostimulant similar to amphetamine) and modafinil in well-rested and sleep-deprived volunteers, analysing 19 and 31 studies respectively. Methylphenidate was found to have a large positive effect (Cohen's d=1.4) on memory; however no statistically significant effects were found on measures of attention, mood and executive functioning. Modafinil administration was found to have a moderate positive effect (d= 0.56) on attention in well rested individuals, with no effect being found for mood, motivation or memory. Single dose modafinil administration in sleep-deprived individuals had significant global effects; positive effect on wakefulness, executive functions (d=3.3) and memory (d=1.22) with no effects on perceived mood. However repeated administration over several days of sleep deprivation was only shown to sustain wakefulness (for up to four days), with no effect compared to placebo on attention and executive functions.

Based on research pertaining to sleep-deprived individuals, modafinil has been sanctioned as an approved substance for the United States military; used to sustain alertness in operational contexts. There is evidence it is useful in maintaining military performance during continuous military operations, with the Air Force authorizing the use of modafinil for dual-seat bomber missions longer than 12 hours in duration. A study by Largarde and Batejat (1995) found volunteers who were kept awake for 60 hours and administered a 200mg dose of modafinil every 8 hours had fewer micro-sleeps than those on placebo and maintained normal rested mental states for up to 44 hours. This was possible without inducing anxiety which is often associated with psychostimulant administration. Modafinil attenuated decrements in reaction time, arithmetic, memory-search, spatial processing, and tracking tasks.

In clinical populations there is evidence that modafinil improves attention and response inhibition in children with ADHD, and improves a number of pre-frontal-dependent cognitive functions in schizophrenia and major depression (Minzenberg & Carter, 2008).

Modafinil as a cognitive enhancer: is it a 'study aid'?

The seemingly beneficial cognitive enhancing effects of modafinil make it appealing as a recreational drug, not only in order to stay awake to 'party' but also as a study aid. Internationally, among university populations, there is evidence that students are buying and selling prescription drugs such as methylphenidate, not for intoxication but in order to improve grades, increase their memory, capacity to learn and their ability to stay awake (Greely et al., 2008). A study in 2005 (McCabe, Knight, Teter, & Wechsler) estimated that almost 7% of students in US universities had used prescription stimulants for cognitive enhancement, with some campuses showing 25% of students had used them in the past year. Modafinil is a new drug that, whilst currently harder to obtain, is appearing on the college black market in the US (Greely et al.), with anecdotal evidence on Australian internet forums suggesting the same pattern occurring nationally. There are radio advertisements in the United States advertising modafinil and armodafinil (the active *R*-enantiomer of modafinil, indicated for the treatment of narcolepsy and shift work disorder), directing listeners to websites providing a free 14 day trial of the drug (Cephalon, 2011).

In 2008, the elite scientific journal Nature ran an online informal survey into reader's use of cognitive enhancing drugs; 1400 people from 60 countries responded (see Figure 2 for ages of sample). Maher found one in five respondents had used drugs for non-medical reasons to stimulate their focus, concentration or memory. For

those who had used cognitive enhancing drugs, 20% of the sample, methylphenidate was the most popular with 62% of users reporting taking it; modafinil was second with 44% of users reporting taking it. The most popular reasons for non-medical use of the stimulants were to improve concentration and focus and to combat jetlag; 'to party' was also the reason given by a number of respondents.

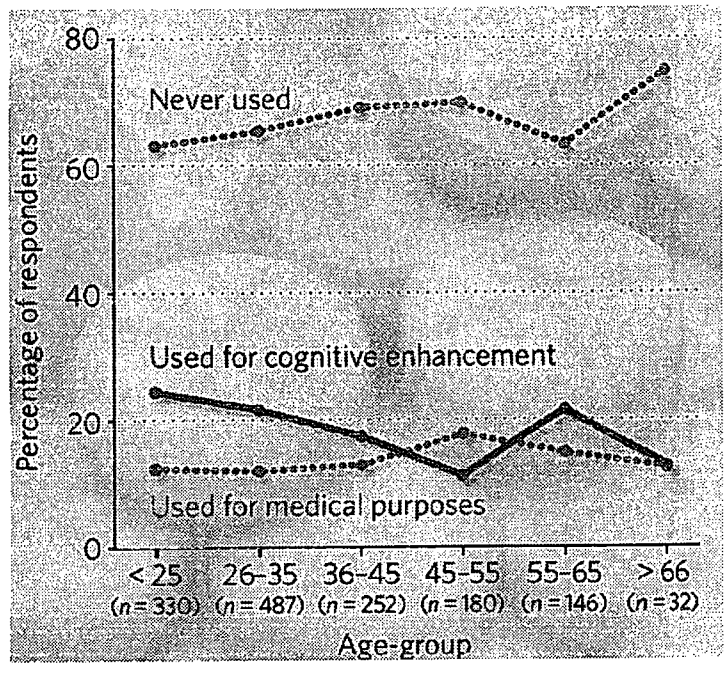

Figure 2. Trends in use of stimulants as neuroenhancers. Results from on online poll by *Nature* (Maher, 2008).

Furthermore, anecdotal internet evidence exists in relation to a number of populations utilizing the cognitive-enhancing and wakefulness-producing effects of the drug. Doctors are using modafinil during night shifts in order to stay awake and alert, and young professionals are utilizing the effects to function effectively throughout the day (November, 2008). Academics mention they use modafinil to combat jet lag (Sahakian & Morein-Zamir, 2007), and newspaper articles discuss modafinil doping in the sporting arena(Feinberg, 2010). However, it seems that off-label and non-prescription use of the drug is high amongst students attending

universities throughout Australia and worldwide, with students dominating discussion boards and forums dedicated to the drug's effects and elicitation (PartyVibeForum, 2011; StudentRoomForum, 2010; Watts, 2011).

Stimulants and driving performance

Despite the previously noted findings, modafinil has not been as widely researched as other stimulants such as caffeine or amphetamine in healthy individuals engaging in real world tasks such as driving. This is of concern as stimulants are often used by drivers who are required to drive long distances to assist with concentration and fatigue levels, with deaths associated with heavy vehicles making up 20% of Australia's road toll (Swann, 2002) A study completed in Victoria, Australia, showed that 4.1% of drivers killed over a 10 year period tested positive to stimulants, with 23% of truck drivers killed testing positive, with an accident risk similar to drivers with a blood alcohol content of 0.1 to 0.15 (Swann, 2002).

Studies examining the effects of stimulant medications on driving skills and related cognitive abilities focus primarily on dexamphetamine; showing inconsistent findings. Dexamphetamine appears to improve performance on some cognitive processes in well rested individuals at low doses and decreases reaction time (Silber et al., 2005), which may suggest an l improvement in driving ability. However dexamphetamine-induced deficits have been reported on divided attention tasks (Mills, Spruill, Kanne, Parkman, & Zhang, 2001) and have been shown to increase risk tasking and impulsive behaviours (Minzenberg & Carter, 2008).Silber et al found dexamphetamine increased traffic rule violations and incorrect signalling, slowed reaction time and decreased overall simulated driving ability. It seems

dexamphetamine can produce 'tunnel vision', also known as perceptual narrowing. This phenomenon decreases an individual's ability to gather information efficiently, and is thought to occur when an individual experiences sympathetic arousal with a consequent restriction of perception to the focal point (Silber et al.). This can be seen as dangerous for driving as it increases the risk of failing to attend to potential hazards that fall outside the driver's attentional focus (e.g. in the periphery).

There is limited research available on the effects of modafinil on simulated driving performance. However Gurtmen, Broadbear and Redman (2008) demonstrated distinct influences on performance compared to dexamphetamine (possibly attributable to their differing neuropsychological effects), with modafinil reducing speed deviation by 14%, reducing lane deviation, off-road incidents and reaction time to a concurrent task on a driving simulator in sleep-deprived participants. However modafinil also caused an overestimation of ability and confidence in self report post drive that is not found with dexamphetamine. This overconfidence effect was also found by Baranski and Pigeau (1997) in sleep deprived individuals, with a trend towards overconfidence in one of six tasks in well rested individuals (Baranski et al., 2004).

In a comparable simulated performance study, it was found that 200mg of modafinil every 4 hours maintained the performance of army pilots in a flight simulator at near-well-rested levels despite 40 hours of continuous wakefulness. Air Force F-117 pilots indicated that 100mg of modafinil administered every 5 hours sustained flight control accuracy to within 27% of baseline levels, whereas performance in the no-treatment condition degraded by over 82% during the latter part of a 37 hour period of continuous wakefulness (Caldwell, Caldwell, Smythe, &

Hall, 2000). Similar beneficial effects were seen on measures of alertness and cognitive performance.

The current study

The current literature surrounding the novel drug modafinil is in support of its alerting and cognitive-enhancing properties, with a great amount of research providing support for its use in preference to dexamphetamine. However, the range of 'off label' uses appears to be rapidly outpacing the growth of literature, with the exact mechanism of action of the drug still unknown. This paucity of knowledge along with the seemingly beneficial effects creates concern for public safety when it comes to its use as a medication and unsanctioned use as a recreational drug or cognitive enhancing drug. The first aim of the current study is to assess acute driving-related cognitive skills and simulated driving performance following a 200mg single dose (the typically prescribed therapeutic dose Stahl, 2011), using measures of driving performance that have been demonstrated to be negatively affected by dexamphetamine. Previous studies have focused on driving performance and modafinil in sleep deprived populations as the common indication for use of the medication is in populations with sleep problems; participants will be well rested in the current study as this has not previously been examined, and there are indications of well-rested individuals using these medications as a cognitive enhancer. A second aim is to assess subjective perception of driving performance following modafinil use. It is hypothesized that, following a single dose of modafinil, driving related skills (sensory-motor reaction time, psychomotor processing speed, focused attention and divided attention) and simulated driving performance will be improved compared to placebo; due to previously reported cognitive enhancing effects of the

drug and its differing neurochemical profile compared to dexamphetamine . There is a very practical use of the results from this study: to assist in education as to modafinil effects on driving, particularly information that can be provided by medical practitioners to patients when prescribing the drug.

Method

Participants

Twenty male participants aged 20-24 were recruited for the study, allowing for the identification of a large effect size (Cohen's f=0.4) at a power of 0.8. Participants were required to have a valid, full driver's license to ensure at least three years driving experience.

Exclusion criteria were: being female, illicit drug users; daily smokers; legitimate use of any medication (prescribed or over the counter); possible alcohol abuse or dependence measured by the Alcohol Use and Disorders Identification Test (AUDIT) (Babor, Higging-Biddle, Saunders, & Monteiro, 2001: defined as ≥19); clinically significant psychological distress as measured by the Kessler Psychological Scale (K10) (Andrews & Slade, 2001: defined as ≥30); individuals at risk of psychosis as identified by the Psychosis Screener (Degenhardt, Wall, Korten & Jablensky, 2005: defined as ≥1) and/or the Schizotypal Personality Questionnaire-Brief (SPQ-B) (Raine, Phil & Benishay, 1991: defined as ≥17); individuals at risk of any contraindication for modafinil use including: anxiety, hypertension, previous psychiatric history (MIMS, 2009).

Participants were recruited through advertisements within the University of Tasmania and peer referral. Interested participants contacted the researcher via SMS or email and were screened at an initial interview. First year psychology students gained course credit and were reimbursed $50 to compensate for time and out-of pocket expenses, with other participants being reimbursed $80. Written informed consent was obtained from all participants prior to testing (Appendix A1 and A2). Ethical approval was provided from the Tasmanian Health and Medical Human Research Ethics Committee.

Materials

Screening Questionnaire. A standardized questionnaire was used in the screening process, including: demographic information, assessment of contraindications to modafinil use; the *AUDIT*; the *Psychosis Screener;* and the *Schizotypal Personality Questionnaire Brief (SPQ-B).*

National Adult Reading Test (NART). The NART (Nelson, 1982) was used as a measure of premorbid intelligence. It requires participants to read aloud 50 words with atypical pronunciation (e.g. debt). Raw scores were converted to predicted Full Scale IQ scores with a mean of 100 and a standard deviation of 15.

Profile of Mood States- Short Form (POMS-SF). The POMS-SF (Shacham, 1983) was used as a measure of mood states at all four testing points. It is a self-administered form of 37 5-point rating scales requiring participants to rate affective states.

Karolinska Sleepiness Scale (KSS). The KSS is a nine-point scale that measures subjective levels of current fatigue. The scale includes verbal labels 'extremely alert' to 'extremely sleepy- fighting sleep'. Higher scores indicate greater levels of fatigue.

*Driving Simulator (*STISIM Drive™ M400*)*. The simulator is a high fidelity system, which provides details of assessed performance at a rate of 20Hz. The simulator consists of a car unit with an adjustable car seat, seatbelt, a dashboard, steering wheel, indicators, brake and accelerator pedal. A realistic driving scenario is displayed across three computer screens, allowing a 140 degree view of the driving environment, including rear and side mirrors. Auditory feedback is provided by speakers and includes the sound of the engine, braking, speeding through corners and when a collision occurred. Whenever a collision occurs, a broken windshield is projected, and the sound of braking glass can be heard. Subsequently, the car is placed back in the middle of the left traffic lane, and subjects can continue their driving test. Each drive includes a scenic, urban and suburban scenarios, allowing drivers to experience low car density areas as well as heavily populated city areas. The following variables were assessed, following protocols by Leung and Starmer (2005) and Lintzeris, Leung, Lenne, Haber and Bruno (2010):

i) Divided attention task; a stimulus is present in each corner of the screen, participants are required to respond when the stimulus changes (e.g. triangle to diamond) by pressing the corresponding buttons positioned to the right of the steering wheel, measuring reaction time and number of correct responses, incorrect responses and no response

ii) Time out of lane (%); participants are asked to drive to the best of their ability and remain in their lane, this variable is the time spent out of the left lane (excluding time during turning events).

iii) Number of centre line crossings; number of times participants cross the centre line in the simulated drive.

iv) Number of collisions/accidents; number of times participants collide with other vehicles and off-road accidents.

v) Gap distance; participants are required to turn right across a lane of oncoming traffic, gap distance is the distance in metres to the closest car when the turn is initiated

vi) Gap time; participants are required to turn right across a lane of oncoming traffic, gap time is the time in seconds to the closest car when the turn is initiated.

vii) Lateral lane deviation (suburban, urban, scenic); the amount of weaving of the vehicle (or how 'wiggly' the car is) is throughout the simulated drive, measured by the standard deviation of the lateral position (SDLP, cm). Differences between active and placebo are regarded relevant if > +2.4 cm (seen after consuming alcohol to reach BAC of 0.05% i.e. the legal limit for driving in many countries.

These provide a comprehensive assessment of driving performance and can assess areas that were identified as deficits following dexamphetamine (Silber et al. 2005).

Occupational Safety Performance Assessment Technology (OSPAT). The OSPAT (OSPAT Pty Ltd., 2005) is an unpredictable tracking task that requires quick reaction time, focused attention and hand-eye coordination. It requires participants to continually return an unpredictably moving cursor to the centre of a circular target presented on a screen, using a track ball. Cursor movement (jitter) is varied based on adaptive staircase procedure in order to avoid ceiling effects. The OSPAT produces a

performance score from an algorithm (subject to commercial confidence) based on reaction time and accuracy. Higher scores indicate greater tracking performance, with the score relating to the greatest amount of jitter that can be reliably responded to.

Visual Analogue Scales (VAS). VAS scales were used to assess perception of alertness, as well as perceived performance on STISIM simulator; driving ability, level of impairment, ability to drive safely, confidence and ability to obey road rules at baseline and after ingestion of 200mg modafinil/placebo. Participants also completed a VAS regarding perceived effects of the drug at the end of each session; strength of drug effect, liking of drug effect, alert level; and intoxication level.

Cambridge Neuropsychological Test Automated Battery (CANTAB) Reaction Time Index (RTI). The RTI is a test of the subjects response to a visual target where the stimulus is either predictable (simple reaction time) or unpredictable (choice reaction time).The participant is required to hold down a press pad button and touch the screen when a yellow dot appears, releasing the button and touching the position of the dot on the screen. The first stage is predictable (the dot requiring a response only ever appearing at a single position), the second stage is unpredictable and the dot may appear in any one of five places. Thirty trials of each of the simple and choice reaction time components of the task are conducted. The duration between initiation of each trial (depressing the press pad) and presentation of the target stimulus is randomly varied in order to avoid expectancy effects.

CANTAB Stop-signal Task (SST). The SST is a response inhibition test. Participants are presented with a stimulus and are required to press a corresponding

key as quickly as possible. On 25% of trials a 'stop' signal is presented soon after stimulus onset, whereby participants are required to withhold their response to the stimuli (blocked so that 4 'stop' signals are presented every 16 trials). The delay time at which participants can reliably inhibit their responses (at 79.5% accuracy) is determined using a double random staircase procedure (mean 'stop' reaction time, SSRT). This can be compared to motor response speed by comparing the speed of participant responses to 'go' trials. The number of direction errors, proportion of successful stops and stop signal delay are also assessed. This test gives a measure of an individual's ability to inhibit a pre-potent response.

CANTAB Rapid Visual Information Processing (RVP). The RVP is a test of sustained attention. In this task a sequence of digits (e.g. 3, 5, 7) is constantly displayed on the right side of a computer monitor. A series of 300 digits are presented in the centre of the monitor at a rate of 80 per minute, the participant is required to press a key whenever a sequence of digits matches the target stimuli displayed on the right of the screen. Total hits, misses, false alarms and correct rejections are measured, along with probability of a 'hit', probability of a false alarm, sensitivity of signal detection, and mean latency (reaction time).

Randomisation and blinding

Randomisation regarding order of placebo and 200mg of modafinil was computer generated by an independent researcher, prior to the enrolment of any participants in the study. After participants were determined as meeting the inclusion criteria and none of the exclusion criteria they were assigned a code based on their sequence of presentation. The orders of sessions had been placed in sealed envelopes

for each participant code prior to enrolment, and in the first experimental session, the envelope for that participant was opened to reveal which drug was to be administered initially. In order to protect the blinding of the experimenters, an external party decided which of the two identically-packaged (white capsule) placebo and active drugs were to be labelled 'blue' or 'pink'; the identity of which of these colours referred to the active drug was protected until the completion of data analysis.

Procedure

Participants were tested in 4.5 hour sessions at the University of Tasmania, completing two treatment sessions (i) placebo tablet and (ii) 200mg modafinil tablet. Participants completed the two sessions at least 1 week apart to reduce traces and any residual effects of modafinil if it was consumed during the first session.

Participants completed the POMS, KSS and VAS (relating to current mood/alertness/driving confidence) followed by the STISIM Drive simulator task, post drive VAS, the OSPAT and the CANTAB tasks. Following these tasks (45 minutes into the testing session) modafinil or placebo was administered to participants. A three hour delay followed, to allow for modafinil to reach peak plasma levels (Wong et al. 1999a) with lunch being consumed in this break; the testing procedure was then repeated. In line with procedures used in neuropsychological testing batteries, the order of test administration remained consistent throughout the study; consequently any fatigue effects were uniform across participants. Participants were required to have a friend collect them post session, received consumer medical information for modafinil (Appendix A3) and instructed not to drive or consume alcohol for the remainder of the day. Please see Table 2 below for detailed test sequence of each session.

Table 2
Detailed Test Sequence of Testing Sessions

Approximate time	Testing session 1 and 2
0 mins	Assess nicotine/caffeine intake
	POMS-SF KSS
	Pre VAS measure
	STISIM Simulator -training drive -assessed drive
	Post VAS measure
	OSPAT x3
	CANTAB (RTI, SST, RVP)
45mins	Ingest pill (modafinil/ placebo)
	Three hour delay (lunch)
3 hrs 45mins	POMS-SF KSS
	Pre VAS measures
	STISIM simulator -assessed drive
	Post VAS measures
	OSPATx3
	CANTAB (RTI, SST, RVP)
4hrs 30mins	VAS relating to perceived drug effects

Note: POMS-SF-profile of mood states short form; KSS-Karolinska sleepiness scale; VAS-visual analogue scale; CANTAB- Cambridge Neuropsychological Test Automated Battery; RTI-reaction time index; SST-stop signal task; RVP-rapid visual information processing

Design

The current study employed a 2 (condition: placebo, modafinil) x 2 (time: baseline, peak) double-blind, placebo-controlled, within subjects design. The dependent variables were performance on the STISIM simulator, CANTAB, OSPAT

and participant's perceived performance. Data analysis was focused on the difference between baseline and peak performance for each condition; this was to enable the most practical information to be gained and interpreted.

Results

This study has adopted the effect size conventions suggested by numerous authors (e.g. Dattalo, 2008; Osteen & Bright, 2010) and have applied the convention of 'small' =.01, 'medium' =.09 and 'large' as .25, given that an impact that contributes to around 10% of the variability in performance is practically meaningful in this context.

Demographic and screening (control) variables

Screening procedures revealed a university educated sample with average intelligence (as measured by the NART). Alcohol use was within safe levels (as measured by the AUDIT), as was risk of psychosis (SPQ) and psychological distress (K10) (Table 3).

Table 3

Means and Standard Deviations for Demographic and Screening Variables

Variable	*M*	*SD*
Sex (% male)	100%	n/a
Age (years)	21.7	1.2
Level of Education (% commenced/completed tertiary)	100%	n/a
Problematic Alcohol Use (AUDIT)	7.2	4.0
Psychological Distress (K10)	12.8	3.2
General Intellectual Functioning (NART)	105.8	5.3

Note: Level of Education has four categories: 7-10, 11-12, tertiary commenced and tertiary completed; AUDIT score range is 0-40, with a score of 19 or more indicating harmful alcohol use (Mackenzie et al. 1996); K10 score range is 10-50, with scores greater than 30 indicating clinical level s of psychological distress (Andrews et al. 2001); SPQ scores range from 0-22, with a score of 17 or more indicating an increased risk of psychosis (Raine, Phil, Benishay, 1995); NART standardised score mean =100 (*SD*=15), with higher scores indicating higher levels of general intellectual function (Nelson, 1982).

Baseline Measures

Participants were compared on variables that had the potential to confound the main analyses, prior to both testing conditions. Caffeine and nicotine intake on day of testing, fatigue at time of testing (Karolinska Sleepiness Scale) and mood disturbance (POMS-SF) did not differ significantly at the beginning of each testing condition (Table 4).

Table 4

Group Performances, Means, Standard Deviations (in parenthesis) and Paired Samples T-Test Results for control variables prior to drug administration (baseline)

Baseline Measure	Modafinil Condition	Placebo Condition	*t*	*p*
Caffeine Intake	0.4 (0.5)	0.4 (0.6)	0.00	1.000
Nicotine Intake	0.0	0.0	n/a	n/a
Fatigue (KSS)	3.5 (1.0)	3.8 (1.3)	1.05	.309
POMS-SF (Total Mood Disturbance)	14.1 (6.0)	15.2 (7.7)	0.75	.461
POMS-SF subscales				
Tension-Anxiety	1.2 (1.4)	1.8 (3.3)	0.96	.350
Depression-Dejection	0.4 (0.9)	0.5 (1.0)	0.19	.853
Anger-Hostility	0.2 (0.5)	0.7 (1.4)	1.52	.144
Vigour-Activity	9.5 (3.3)	8.7 (3.6)	1.31	.205
Fatigue-Inertia	2.2 (1.6)	3.1 (2.6)	1.41	.175
Confusion-Bewilderment	0.6 (1.1)	0.6 (0.9)	0.18	.858

Note: * statistical significance at $p \leq 0.05$; Caffeine/nicotine intake refers to number of caffeinated/nicotine products consumed on day of testing, prior to the testing session; KSS score range is 1-9, with high scores indicating higher level of fatigue; POMS-SF Total Mood Disturbance score range is 0-148, with high scores indicating higher levels of overall mood disturbance; For all POMS-SF subscales, high scores indicate higher levels of mood disturbance; Tension-Anxiety subscale score range is 0-24, Depression- Dejection subscale range is 0-32, Anger-Hostility subscale score range is 0-28 , Vigour-Activity subscale score range is 0-24 , Fatigue-Inertia subscale score range is 0-20, Confusion-Bewilderment subscale score range is 0-20.

Mood Variables

A 2 (condition: modafinil, placebo) x 2(time: baseline, peak) repeated measures ANOVA was conducted to examine mood for each testing session, as measured by the KSS and the POMS-SF. There was a main effect for time, $F(1, 19) = 27.85$, $p \leq .001$, with total mood disturbance being higher at baseline (M=14.63,

SD=6.04) than peak (*M*=11.43, *SD*=5.05). A main effect for time was also found for levels of tension-anxiety, $F(1, 19) = 7.94$, $p = .011$, being higher at baseline (*M*=1.45, *SD*=2.06) than peak drug (*M*=0.68, *SD*=1.12) (Table 5).

There was a trend towards a significant interaction between condition and time for the anger-hostility subscale, $F(1, 19) = 3.93$, $p = .062$, with a medium effect size ($\eta^2_p = .171$). Using partial eta squared values to breakdown this interaction, a medium effect size was found between baseline and peak for the placebo condition ($np^2 = .212$), with levels of anger-hostility being significantly higher at Placebo baseline (*M*=0.70, *SD*=1.38) than placebo peak (*M* =0.10, *SD*=0.45). No effect was found for the modafinil condition ($\eta^2_p = .001$) (Table 6).

Table 5

Means, Standard Deviations (in parenthesis) and Partial Eta Squared for KSS and Profile of Mood States- Short Form as a Function of Drug Condition and Time

	Modafinil			Placebo		
	Baseline	Peak	η^2_p	Baseline	Peak	η^2_p
Fatigue (KSS)	3.47 (1.02)	3.63 (1.57)	.008	3.84 (1.34)	3.89 (1.37)	.001
POMS-SF (Total mood disturbance)	14.05 (6.01)	10.95 (5.19)	.263	15.20 (7.74)	11.90 (5.81)	.328
POMS-SF subscales						
Tension-Anxiety	1.15 (1.35)	0.50 (0.95)	.197	1.75 (3.26)	0.85 (1.53)	.159
Depression-Dejection	0.40 (0.88)	0.15 (0.67)	.083	0.45 (1.00)	0.25 (0.72)	.040
Anger-Hostility	0.20 (0.52)	0.20 (0.62)	.000	0.70 (1.38)	0.10 (0.45)	.212
Vigour-Activity	9.50 (3.93)	8.15 (4.58)	.085	8.70 (3.61)	7.10 (3.84)	.210
Fatigue-Inertia	2.20 (1.61)	1.60 (2.04)	.095	3.05 (2.63)	2.90 (3.42)	.003
Confusion-Bewilderment	0.60 (1.05)	0.35 (0.67)	.054	0.55 (0.89)	0.70 (1.08)	.021

Note: KSS score range is 1-9, with high scores indicating higher level of fatigue; POMS-SF Total Mood Disturbance score range is 0-148, with high scores indicating higher levels of overall mood disturbance; For all POMS-SF subscales, high scores indicate higher levels of mood disturbance; Tension-Anxiety subscale score range is 0-24, Depression- Dejection subscale range is 0-32, Anger-Hostility subscale score range is 0-28 , Vigour-Activity subscale score range is 0-24 , Fatigue-Inertia subscale score range is 0-20 , Confusion-Bewilderment subscale score range is 0-20.

Table 6

Repeated Measures ANOVA Results and Partial Eta Squared for KSS and Profile of Mood States- Short Form as a Function of Drug Condition and Time

	Condition		Time		Condition*Time		η^2_p
	F	*P*	*F*	*P*	*F*	*p*	
Fatigue (KSS)	1.15	.297	0.11	.743	0.70	.793	.004
POMS-SF (total mood disturbance)	1.57	.226	27.85	**.000*** Baseline>Peak	0.01	.918	.001
POMS-SF subscales							
Tension-Anxiety	1.47	.240	7.94	**.011*** Baseline>Peak	0.19	.669	.010
Depression-Dejection	0.14	.711	2.34	.143	0.03	.867	.002
Anger-Hostility	0.86	.366	2.92	.104	3.93	.062	.171
Vigour-Activity	2.90	.105	3.68	.070	0.09	.769	.005
Fatigue-Inertia	3.55	.075	1.12	.304	0.36	.557	.018
Confusion-Bewilderment	0.77	.390	0.09	.766	1.42	.248	.070

Note: * denotes statistical significance at $p<0.05$; Degrees of freedom for all analyses = 1, 19.

At the conclusion of each testing session, participants completed a visual analogue scale relating to perceived effects of the drug consumed, they were also asked whether they thought they had ingested modafinil or placebo (see Table 7). Participants were not reliably able to determine which condition they were in, with 35% of participants in both conditions reporting they had ingested modafinil..

However there was a significant difference for level of alertness between conditions, t (19) =3.94, p=.001, with participants reporting feeling more alert after ingesting Modafinil (M=6.47, SD=2.27) than after ingesting Placebo (M=4.55, SD=1.70); consistent with the effect of the drug.

Table 7

Means, Standard Deviations (in parenthesis) and Paired Samples t-Test Results for Perceived Drug Effects as measured by a Visual Analogue Scale

	Modafinil Condition	Placebo Condition	*t*	*p*
Strength	2.67 (2.85)	2.16 (2.76)	0.59	.562
Liking	5.07 (1.47)	4.61 (1.47)	0.88	.392
Alert	6.47 (2.27)	4.55 (1.70)	3.94	**.001*** Modafinil>Placebo
Intoxication	0.92 (1.37)	1.76 (2.20)	1.65	.116
Ingested modafinil	35%	35%	n/a	n/a

Note: * denotes statistical significance at $p<0.05$; 19.'Ingested modafinil' refers to the percent of people who thought they had ingested modafinil at the completion of each testing condition. VAS score range 0-10, 0= strongly disagree, 10=strongly agree

Cognitive Measures

Tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Occupational Safety Performance Assessment Technology (OSPAT) were used to measure the possible cognitive effects of modafinil. Two way [2 (condition: modafinil, placebo) x 2(time: baseline, peak)] repeated measures ANOVAs were conducted to examine possible effects.

There were no significant main effects or interactions for the RTI (Table 9). However there was a trend towards a significant condition x time interaction for simple error rate (premature responses), $F(1, 19) = 3.71$, $p=.069$, with a medium effect size ($\eta^2_p=.163$). Partial eta squared values were used to breakdown this interaction. A medium magnitude effect size was found between baseline and peak for the placebo condition ($\eta^2_p=.150$), with higher numbers of premature responses

made at placebo baseline (*M*=0.20, *SD=0.41*), than placebo peak (*M* = 0.05, *SD*= 0.22). A small effect size was found between baseline and peak for the modafinil condition (η^2_p=.063), with higher numbers of premature responses made at modafinil peak (*M*=.30, *SD*=0.66), than modafinil baseline (*M*=0.10, *SD*=0.31). Whilst this may appear to show that modafinil increases impulsivity and decreases inhibition, the fact this finding did not carry over on a more complex measure of response inhibition (SSRT) decreases the validity of this trend on the RTI. It should also be noted that these findings are not practically relevant; with the error rate fluctuating by 0.15 and 0.20 respectively over 30 trials, where a possible 30 errors could be made (Table 8).

Table 8

Means, Standard Deviations (in parenthesis) and Partial Eta Squared for CANTAB Reaction Time Index (RTI) as a Function of Drug Condition and Time

	Modafinil			Placebo		
	Baseline	Peak	η^2_p	Baseline	Peak	η^2_p
Simple Reaction Time (ms)	267.63 (32.45)	261.25 (36.40)	.051	263.01 (32.13)	263.99 (31.24)	.002
Choice Reaction Time (ms)	286.43 (32.59)	275.43 (32.88)	.207	286.45 (35.68)	282.07 (25.09)	.030
Simple Movement Time (ms)	304.93 (49.23)	299.82 (46.86)	.015	305.98 (47.31)	309.10 (60.03)	.008
Choice Movement Time (ms)	472.95 (675.28)	304.73 (44.51)	.063	314.80 (50.83)	301.73 (81.02)	.032
Simple Accuracy (out of 30)	29.80 (0.52)	29.60 (0.75)	.040	29.60 (0.76)	29.55 (0.76)	.003
Choice Accuracy (out of 30)	29.75 (0.44)	29.90 (0.31)	.064	29.75(0.64)	28.15 (6.67)	.057
Simple Error rate$^{\Delta}$	0.10 (0.31)	0.30 (0.66)	.067	0.20 (0.41)	0.05 (0.22)	.150
Choice Error Rate$^{\Delta}$	0.05 (0.22)	0.00 (0.00)	.050	0.03 (0.15)	1.15 (4.69)	.056

Note: reaction times are in milliseconds; $^{\Delta}$ Error rate indicates premature response, out of 30 possible trials

Table 9

Repeated Measures ANOVA Results and Partial Eta Squared for CANTAB Reaction Time Index (RTI) as a Function of Drug Condition and Time

	Condition		Time		Condition*Time		η^2_p
	F	*p*	*F*	*p*	*F*	*p*	
Simple Reaction Time	0.08	.780	0.91	.352	0.55	.469	.028
Choice Reaction Time	0.84	.372	3.19	.090	1.13	.300	.056
Simple Movement Time	0.22	.644	0.02	.890	0.57	.462	.029
Choice Movement Time	1.10	.307	1.56	.228	1.01	.329	.050
Simple Accuracy	0.92	.349	0.92	.349	0.20	.659	.010
Choice Accuracy	1.35	.260	0.92	.350	1.37	.257	.067
Simple Error rate$^{\Delta}$	0.46	.505	0.06	.804	3.71	.069	.163
Choice Error Rate$^{\Delta}$	1.17	.293	1.03	.322	1.24	.280	.061

Note: * denotes statistical significance at $p<0.05$; Degrees of freedom for all analyses = 1, 19; $^{\Delta}$ Error rate indicates premature response

For the SST, a significant main effect for time was found, $F(1, 19) = 12.22$, $p = .002$, with reaction time on GO trials being slower at baseline ($M = 351$ ms, $SD=83$) than at peak ($M = 337$ ms, $SD=75$). A significant condition x time interaction was found for stop signal reaction time, $F(1, 19) = 5.52$, $p=.030$, with reaction time being significantly faster at modafinil peak ($M = 129$ ms, $SD = 19$) than modafinil baseline ($M = 141$ ms, $SD = 30$). There was no such effect between baseline and peak for the placebo condition ($\eta^2_p=.001$).

Table 10

Means, Standard Deviations (in parenthesis) and Partial Eta Squared for CANTAB Stop Signal Task (SST) as a Function of Drug Condition and Time

	Modafinil			Placebo		
	Baseline	Peak	η^2_p	Baseline	Peak	η^2_p
Direction errors	4.25 (3.43)	6.00 (4.88)	.175	6.15 (6.43)	7.20 (8.04)	.079
Proportion of successful stops	0.45 (0.05)	0.45 (0.05)	.012	0.46 (0.06)	0.45 (0.05)	.065
Reaction Time on GO Trials (ms)	344.80 (82.28)	332.79 (70.22)	.116	357.50 (92.99)	341.83 (83.69)	.269
Stop Signal Delay (SSD) (ms)	200.70 (76.13)	193.21 (64.95)	.043	204.62 (82.59)	196.17 (78.17)	.078
Stop Signal Reaction Time (SSRT) (ms)	141.15 (29.55)	129.24 (19.09)	.243	134.64 (31.89)	135.38 (26.84)	.001

Note: 'Direction errors' lower score indicates better performance; 'proportion of successful stops' higher score indicates better performance; 'RT on GO trials' is in milliseconds, lower score indicates better performance; 'SSD' refers to the stop signal delay at which the subject was able to stop 50% of the time, lower scores indicate better performance; 'SSRT' is an estimate of the length of time between the go stimulus and the stop stimulus at which the subject is able to successfully inhibit their responses on 50% of trials, lower scores indicate better performance.

Table 11

Repeated Measures ANOVA Results and Partial Eta Squared for CANTAB Stop Signal Task (SST) as a Function of Drug Condition and Time

	Condition		Time		Condition*Time		η^2_p
	F	*p*	*F*	*p*	*F*	*p*	
Direction Errors	1.88	.186	3.67	.070	0.66	.427	.034
Proportion of successful stops	0.01	.915	0.20	.657	0.81	.380	.041
Reaction Time on GO Trials	1.35	.259	12.22	**.002*** Baseline>Peak	0.11	.746	.006
Stop Signal Delay (SSD)	0.20	.660	2.49	.131	0.01	.930	.000
Stop Signal Reaction Time (SSRT)	0.00	.975	2.10	.164	5.52	**.030*** Modafinil baseline>Modafinil peak	.225

Note: * denotes statistical significance at $p<0.05$; Degrees of freedom for all analyses = 1, 19; 'SSD' refers to the stop signal delay at which the subject was able to stop 50% of the time; 'SSRT' is an estimate of the length of time between the go stimulus and the stop stimulus at which the subject is able to successfully inhibit their responses on 50% of trials.

For the RVP no significant interactions or trends towards a significant interaction were found. A significant man effect for time was found for total hits, F (1, 19) =11.01, p=.004, with higher scores being found at peak (M=22.73, SD=3.18) than baseline (M=20.73, SD=3.71). A significant main effect for time was also found for total misses, F (1, 19) =10.80, p=.004, with more misses being found at baseline (M = 6.25, SD =3.71) than at peak (M=4.53, SD =3.18). Further significant main effects were found for total correct rejections, F(1, 19)=9.26, p=.007, with performance being better at peak (M=261.80 , SD=7.60) than baseline (M=258.28, SD=7.69); probability of a 'hit', F(1, 19)=10.85, p=.004, with higher scores at peak (M=0.83, SD=0.13) then baseline (M=0.77, SD=0.13); and signal detection measure,

$F(1, 19) = 11.58, p = .003$, with higher scores being found at peak ($M = 0.96$, $SD = 0.045$) than baseline ($M = 0.94$, $SD = 0.04$).

Table 12

Means, Standard Deviations (in parenthesis) and Partial Eta Squared for CANTAB Rapid Visual Processing (RVP) as a Function of Drug Condition and Time

	Modafinil			Placebo		
	Baseline	Peak	η^2_p	Baseline	Peak	η^2_p
Total Hits	20.85 (4.43)	22.65 (3.54)	.306	20.60 (4.51)	22.30 (3.69)	.216
Total False Alarms	0.75 (0.79)	1.25 (1.37)	.208	1.30 (1.42)	1.20 (1.11)	.003
Total Correct Rejections	295.05 (9.17)	262.00 (8.83)	.215	257.50 (9.11)	261.60 (8.29)	.231
A Prime	0.94 (0.04)	0.96 (0.03)	.272	0.94 (0.04)	0.96 (0.03)	.246
B Double Prime	0.95 (0.05)	0.81 (0.47)	.089	0.83 (0.48)	0.94 (0.05))	.053
Mean Latency	394.41 (88.17)	382.87 (91.23)	.031	389.19 (91.80)	370.29 (78.78)	.173

Note: 'Total hits' represents the number of occasions upon which the target sequence is correctly responded to, higher scores indicate better performance; '; 'Total false alarms' records the number of times the subject responds outside the response window of a target sequence, lower scores indicate better performance; 'total correct rejections' is the number of stimuli correctly rejected, higher scores indicate better performance; 'A prime' is the signal detection measure of sensitivity to the target regardless of response tendency, a measure of how good the subject is at detecting target sequences, scores range from 0.00 to 1.00, higher scores indicate better performance; 'B double prime' is the tendency to respond regardless of whether the target response is present, higher scores indicate better performance; 'Mean latency' is mean time taken to respond in milliseconds, lower scores indicate better performance.

Table 13

Repeated Measures ANOVA Results and Partial Eta Squared for CANTAB Rapid Visual Processing (RVP) as a Function of Drug Condition and Time

	Condition		Time		Condition*Time		η^2_p
	F	*p*	*F*	*p*	*F*	*p*	
Total Hits	0.13	.728	11.01	**.004*** Peak>Baseline	0.01	.910	.001
Total False Alarms	0.91	.353	0.81	.379	1.58	.225	.077
Total Correct Rejections	0.32	.581	9.26	**.007*** Peak>Baseline	0.34	.566	.018
A Prime	0.90	.766	11.58	**.003*** Peak>Baseline	0.07	.793	.004
B Double Prime	.002	.967	0.68	.798	2.50	.133	.135
Mean Latency	0.63	.438	2.82	.110	0.18	.673	.010

Note: * denotes statistical significance at $p<0.05$; Degrees of freedom for all analyses = 1, 19; 'Total hits' represents the number of occasions upon which the target sequence is correctly responded to; 'Total false alarms' records the number of times the subject responds outside the response window of a target sequence; 'total correct rejections' is the number of stimuli correctly rejected; 'A prime' is the signal detection measure of sensitivity to the target regardless of response tendency, a measure of how good the subject is at detecting target sequences; 'B double prime' is the tendency to respond regardless of whether the target response is present,; 'Mean latency' is mean time taken to respond

A significant main effect for time was found for the OSPAT score, F (1, 19) =7.76, p=.012, with performance being better at peak (M=14.77, SD=1.43) than at baseline (M=14.40, SD=1.34). No higher order effects were apparent.

Table 14

Means, Standard Deviations (in parenthesis) and Partial Eta Squared for OSPAT as a Function of Drug Condition and Time

	Modafinil			Placebo		
	Baseline	Peak	η^2_p	Baseline	Peak	η^2_p
OSPAT	14.51 (1.35)	14.90 (1.28)	.217	14.29 (1.63)	14.64 (1.79)	.148

Note: higher scores indicate better performance.

Table 15

Repeated Measures ANOVA Results and Partial Eta Squared for OSPAT Performance as a Function of Drug Condition and Time

	Condition		Time		Condition*Time		η^2_p
	F	*p*	*F*	*p*	*F*	*p*	
OSPAT	0.81	.380	7.76	**.012*** Peak>Baseline	0.02	.885	.001

Note: * denotes statistical significance at $p<0.05$; Degrees of freedom for all analyses = 1, 19

STISIM Driving Measures

A 2(condition: modafinil, placebo) x 2(time: baseline, peak) repeated measures ANOVA was performed to determine whether measures taken from performance on the STISIM driving simulator differed between conditions.

A number of main effects for time were found in STISIM driving measures. A significant main effect for time was found for number of 'no response' on the divided attention task, $F(1, 19) = 5.59$, $p=.029$, with scores at baseline ($M=1.08$, $SD=0.76$) higher than at peak ($M=0.55$, $SD= 0.85$). A significant main effect for time was found for number of centre crossings, $F(1, 19) =5.02$, $p=.037$, with more

crossings occurring at baseline (*M*=15.33, *SD*= 7.42) compared to peak (*M*=13.85, *SD*=7.96). A significant main effect for time was also found for number of collisions, *F* (1, 19) =4.75, *p*=.042, with more collisions made at baseline (*M* = 0.33, *SD*=0.36) then at peak (*M*=0.13, *SD*=0.22) (Table 16 and 17).

A significant condition x time interaction was found for lateral lane deviation during the scenic component of the scenario (low traffic density), *F* (1, 19) =4.77, *p*=.042. Follow up analysis revealed no significant differences within the interaction, consequently partial eta squared values were used to breakdown the interaction. A medium effect size was found between baseline and peak for the modafinil condition (η^2_p=.108), with less deviation found at modafinil peak (*M*=0.25, *SD*=0.06) than at modafinil baseline (*M*=0.27, *SD*=0.06). For placebo, lateral lane deviation increased (worsened) from baseline (*M*=0.26, *SD*=0.06) to peak (*M*=0.28, *SD*=0.09) (η^2_p=.103) (Table 16 and 17).

A trend towards a significant condition x time interaction for number of incorrect divided attention responses was found, *F* (1, 19) =3.31, *p*=.085. Partial eta squared values were used to further breakdown this interaction. A medium effect size was found between baseline and peak for the placebo condition (η^2_p=.180), with a higher number of incorrect responses being made at placebo baseline (*M*=0.95, *SD*=1.50) compared to placebo peak (*M*=0.35, *SD*=0.59); no such effect existed between baseline and peak for the modafinil condition (η^2_p =.005). A trend towards a significant condition x time interaction for number of centre crossings was found, *F* (1, 19) =3.77, *p*=.067. Partial eta squared values were used to further breakdown this interaction. A large effect size was found between baseline and peak for the modafinil condition (η^2_p=.370), with significantly fewer centre crossings at modafinil peak (*M*= 12.35, SD=9.14) compared to modafinil baseline (*M*=15.35, *SD*=8.44). No

such effect existed between baseline and peak for the placebo condition (η^2_p=.000) (Table 16 and 17).

Table 16

Means, Standard Deviations (in parenthesis and Partial Eta Squared) for STISIM Driving Measures as a Function of Drug Condition and Time

	Modafinil			Placebo		
	Baseline	Peak	η^2_p	Baseline	Peak	η^2_p
Reaction Time for Correct DA (s)	1.53 (0.33)	1.39 (0.31)	.238	1.44 (0.31)	1.43 (0.38)	.006
Number of DA Correct	21.05 (1.82)	21.40 (1.50)	.022	20.30 (2.41)	21.45 (1.82)	.148
Number of DA Incorrect	0.65 (1.18)	0.75 (1.21)	.005	0.95 (1.50)	0.35 (0.59)	.180
Number of DA No Response	0.85 (1.27)	0.40 (0.75)	.131	1.30 (1.56)	0.70 (1.59)	.109
Time out of Lane (%)	11.47 (8.55)	9.16 (7.81)	.161	12.04 (9.14)	12.43 (10.62)	.004
No. of Centre Crossings	15.35 (8.44)	12.35 (9.14)	.370	15.30 (7.90)	15.35 (9.22)	.000
No. of Collisions	0.25 (0.44)	0.10 (0.31)	.090	0.40 (0.60)	0.15 (0.37)	.114
Gap Distance (ft)	1936.45 (1481.84)	2491.72 (1195.35)	.177	2124.46 (1414.52)	2305.34 (1328.07)	.017
Gap Time (s)	625.49 (498.01)	812.21 (401.59)	.177	687.84 (476.66)	749.95 (445.52)	.018
Lateral Lane Deviation (scenic)	0.27 (0.06)	0.25 (0.06)	.108	0.26 (0.06)	0.28 (0.09)	.103
Lateral Lane Deviation (suburban)	0.56 (0.19)	0.54 (0.18)	.052	0.56 (0.21)	0.55 (0.15)	.007
Lateral Lane Deviation (urban)	0.28 (0.09)	0.27 (0.07)	.008	0.25 (0.07)	0.28 (0.12)	.208

Note: DA indicates divided attention task; Reaction time is in seconds, lower scores indicate better performance; Gap Time and Gap Distance are a measure of gap acceptance when turning against oncoming traffic.

Table 17

Repeated Measures ANOVA Results and Partial Eta Squared for STISIM Driving Measures as a Function of Drug Condition and Time

	Condition		Time		Condition*Time		η^2_p
	F	*p*	*F*	*p*	*F*	*p*	
Reaction Time for Correct DA	0.12	.749	4.04	.059	2.24	.151	.106
Number of DA Correct	0.56	.462	2.98	.101	1.05	.318	.052
Number of DA Incorrect	0.08	.785	1.02	.325	3.31	.085	.148
Number of DA No Response	0.84	.370	5.59	**.029*** Baseline>Peak	0.09	.769	.005
Time out of Lane (%)	1.24	.279	1.22	.283	1.87	.187	.090
No. of Centre Crossings	0.80	.381	5.02	**.037*** Baseline>Peak	3.77	.067	.165
No. of Collisions	0.79	.385	4.75	**.042*** Baseline>Peak	0.24	.629	.012
Gap Distance	0.00	.998	2.94	.107	0.66	.430	.042
Gap Time	0.00	1.00	2.99	.104	0.65	.432	.042
Lateral Lane Deviation (scenic)	0.12	.729	0.00	1.00	4.77	**.042***	.201
Lateral Lane Deviation (suburban)	0.05	.826	0.77	.390	0.04	.850	.002
Lateral Lane Deviation (urban)	0.29	.595	3.03	.098	1.64	.216	.079

Note: * denotes statistical significance at $p<0.05$; Degrees of freedom for all analyses = 1, 19; DA indicates divided attention task; Gap Time and Gap Distance are a measure of gap acceptance when turning against oncoming traffic.

Subjective Performance (Willingness to Drive) Measures

A 2 (condition: modafinil, placebo) x 2 (performance feedback: pre-drive, post-drive) repeated measures ANOVA was performed to examine subjective performance. A significant main effect for performance feedback on levels of

alertness was found, F (1, 19) = 7.50, p=.013, with higher levels of alertness found post-drive (M=8.25, SE=1.10) compared to pre-drive (M=7.62, SE=1.64). A significant main effect for performance feedback on perceived ability was also found, F (1, 19) =7.33, p=.014, with higher perceived ability post-drive (M=8.61, SE=0.88) compared to pre-drive (M=8.14, SE=1.38). A trend towards a significant condition x performance feedback interaction was found, F (1, 19) =3.59, p=.074, partial eta squared values were used to breakdown this interaction. A small effect size was found between baseline and peak for both the modafinil condition (η^2_p=.020) and placebo condition (η^2_p=.092); therefore this finding does not appear to be practically relevant (Table 18 and 19).

Table 18

Means, Standard Deviations (in parenthesis) and Partial Eta Squared for VAS Measures as a Function of Drug Condition and Performance Feedback

	Modafinil			Placebo		
	Pre drive	Post drive	η^2_p	Pre drive	Post drive	η^2_p
Alert	7.84 (1.73)	8.41 (1.25)	.118	7.41 (1.93)	8.09 (1.45)	.325
Ability	8.30 (2.00)	8.74 (0.97)	.058	7.99 (1.53)	8.48 (1.18)	.155
Impaired	8.66 (1.17)	8.60 (1.17)	.002	7.94 (1.68)	8.34 (1.39)	.078
Safely	8.85 (0.93)	8.69 (1.15)	.020	8.23 (1.78)	8.67 (1.06)	.092
Confident	8.72 (1.08)	8.90 (1.03)	.033	8.27 (1.59)	8.80 (0.84)	.209
Obey road rules	8.65 (1.05)	9.04 (1.22)	.069	8.37 (1.64)	8.34 (1.70)	.000

Note: VAS score range 0-10, 0= strongly disagree, 10=strongly agree

Table 19

Repeated Measures ANOVA Results and Partial Eta Squared for VAS Measures as a Function of Drug Condition and Performance Feedback

	Condition		Performance Feedback		Condition* Performance Feedback		η^2_p
	F	*p*	*F*	*p*	*F*	*p*	
Alert	1.60	.222	7.50	**.013***	.073	.790	.004
Ability	1.05	.319	7.33	**.014***	.010	.920	.001
Impaired	2.65	.120	0.59	.454	1.39	.253	.068
Safely	1.67	.212	0.34	.565	3.59	.074	.159
Confident	1.55	.228	4.05	.059	1.41	.250	.069
Obey road rules	3.56	.074	0.43	.522	0.62	.442	.031

Note: * denotes statistical significance at $p<0.05$; Degrees of freedom for all analyses = 1, 19. VAS score range 0-10, 0= strongly disagree, 10=strongly agree

Discussion

The aim of the current study was to assess acute driving-related cognitive skills and simulated driving performance following a 200mg single dose of modafinil, using measures of driving performance that have been demonstrated to be negatively affected by dexamphetamine. Driving related cognitive skills were assessed through the reaction time index (RTI), stop signal task (SST), rapid visual information processing (RVP) and OSPAT, with driving performance being measured by the STISIM driving simulator. The hypothesis that, following a single dose of modafinil, both driving related cognitive skills and simulated driving performance would be improved compared to placebo was partially supported. There was a significant condition x time interaction for stop signal reaction time

(CANTAB-SST), with reaction time being significantly faster at peak levels of modafinil than baseline (η^2_p=.243), with no such finding on placebo (η^2_p=.001). There was a significant condition x time interaction for lateral lane deviation (scenic – low traffic density), with less lateral lane deviation on the STISIM simulator at modafinil peak than modafinil baseline (η^2_p=.108), while for placebo lateral lane deviation increased (worsened) from baseline to peak (η^2_p=.108). There was also a trend towards a significant condition x time interaction (at a large effect size), with the number of centre lane crossings on the STISIM simulator being significantly lower at peak levels of modafinil compared to baseline (η^2_p=.370) but there being no such effect for placebo (η^2_p=.010).

It is important to note the successfulness of the blinding procedure applied in this study. Participants were unable to reliably determine which drug they had ingested, with one-third believing they were on the active drug in both the placebo and active drug conditions. As such, the following results can be interpreted as reliable.

Modafinil and how it affects mood

Main effects of time existed for POMS-SF total mood disturbance and the tension-anxiety subscale, with higher levels at baseline than peak, regardless of drug condition. This may be explained by anticipatory anxiety (Chua, Krams, Toni, Passingham, & Dolan, 1999) prior to engaging in challenging tasks.

It has been widely reported that modafinil is a wakefulness promoting drug (Banerjee, Vitiello, & Grunstein, 2004; Baranski et al., 2004; MIMS, 2009; Repantis et al., 2010); this was supported by the current study. Levels of alertness as measured

by a 100mm visual analogue scale, showed a significant effect of modafinil in increasing alertness compared to placebo. This self report measure was taken at the completion of the testing procedure, approximately 3hours 45 minutes after drug ingestion. No such differences were evident on other measures of alertness collected using visual analogue scales, KSS or the POMS-SF fatigue-inertia subscale at 3 hours post drug administration , despite the fact these measures are sensitive to the impact of sustained wakefulness (Caldwell, Caldwell, Smith, & Brown, 2004).

One possible explanation for the discrepancies in alertness findings between visual analogue scales, KSS and the POMS-SF may be an alteration in the time taken to reach peak plasma levels. Modafinil is reported to take between 2-4 hours to reach peak plasma levels (Wong et al., 1999), which is why the current study conducted post drug testing procedures at 3hours post administration (consistent with other research in this area). However in order to maintain a homogenous testing protocol participants were required to consume lunch post drug ingestion. The presence of food in the gastrointestinal tract may have slowed the rate of modafinil absorption (Wong et al., 1999) and therefore affected the time to peak plasma levels, explaining why the significant increase in alertness existed at 3hours 45minutes post drug and not at 3hours.

Another explanation for this may be that modafinil induced alertness is modulated by the demand of the task. This reasoning is based on the experience of many participants in the current study. Levels of alertness, as measured by the VAS, KSS and the POMS-SF, were taken at 3 hours post drug administration, after the relaxation period and prior to post-drug cognitive testing. However, anecdotal evidence appeared to show participants feeling more alert post STISIM driving

simulation, with many commenting on how alert they felt when getting off the simulator, approximately 15 minutes later.

Participants were unable to reliably determine whether they had ingested modafinil or placebo, with 35% of participants in both conditions reporting that they had ingested modafinil. However anecdotal evidence at the completion of the second testing session revealed that participants thought determining conditions was easier once they had experienced both placebo and modafinil administration; with 40% of participants feeling they had made a 'mistake' at the end of their first testing session when reporting what they had ingested. It should be noted that 75% of these participants would have been correct in identifying the conditions if they had been allowed to change their first response.. Side effects in the modafinil condition were rare in the current study, one participant reported feeling dizzy for a short period of time and another experienced a mild headache, requiring paracetamol administration; interestingly in the second case the participant speculated he had ingested placebo.

Modafinil and measures of cognition (driving related skills)

It was hypothesized that modafinil would improve performance on cognitive tasks from the CANTAB and OSPAT. This was generally not the case, with few significant or trends towards significant interactions being found.

A significant condition x time interaction was found for stop signal reaction time (SSRT) on the stop signal task from the CANTAB, with reaction time being faster at modafinil peak compared to modafinil baseline, with no such effect being found on placebo. This suggests modafinil decreases impulsivity, by enhancing one's ability to inhibit pre-potent responses.. Mean speed of responding was the same

regardless of the drug condition, with no differences between modafinil and placebo on the mean 'go' reaction time being found. This shows that improved response inhibition on modafinil as measured by the SSRT cannot be attributed to slower responding on the 'go' trials.

This was also found by Turner et al. (2003) in a study of 60 non-sleep deprived adults. A dose-dependent effect on SSRT was found, with those who ingested a 200 mg single dose of modafinil performing optimally, compared to 100 mg of modafinil and placebo (those who ingested 100mg of modafinil also performed better than those in the placebo condition). No differences were found between groups on reaction time for 'go' trials, however 200 mg of modafinil led to the least number of direction errors made; the current study did not find this (possibly due to ceiling effects in this well-rested participant sample). The same research group again found enhanced SSRT performance after a single dose of 200 mg of modafinil compared to placebo in a study of 20 adult ADHD patients (Turner, Clark, Dowson, Robbins, & Sahakian, 2004).

Whilst the positive effect modafinil appears to have on inhibiting prepotent responses is consistently found, this is not the case for dexamphetamine. In relation to risk taking behaviours and impulsivity amphetamines are known to be effective in the treatment of ADHD and therefore reducing impulsivity and inattention. However when it comes to controlled experimental research, findings are varied. De Wit, Enggasser and Richards (2002) found dexamphetamine decreases impulsive responses as measured by SSRT, however this was only the case for those people who had comparably slow SSRTs at baseline. Other studies have reported increases in impulsive behaviours and SSRTs following dexamphetamine administration (Evenden & Ryan, 1996; Hurst, 1962; Hurst, Weidner, & Radlow, 1967). Therefore

whilst a relationship between dexamphetamine and impulsivity clearly exists, it appears to be complex and possibly dose- or population- specific. This does not appear to be the case for modafinil with a clear enhancing effect of the drug.

SSRT performance, and consequently inhibitory control, is a cognitive ability that underlies safe driving; executive planning and the interaction with traffic when driving enables adaptive inhibition when required. Enhanced SSRT performance as seen in the modafinil condition demonstrates participants improved ability to inhibit a prepotent response and can be seen as improved behavioural impulsivity and hence reduced riskiness. A study by Jongen Brijs, Komlos, Brijs and Wets (2011) found a medium correlational relationship (r=.443, p=.001) between the measure of inhibition (SSRT) and standard deviation of lateral lane position (SDLP), that is how variable (or 'wiggly') the driver is within the lane. The researchers found that with increased inhibitory control there was a decrease in SDLP. This demonstrates that improved SSRT leads to safer driving when it comes to decreasing lane deviation. The skills underlying SSRT may also result in improved performance when it comes to avoiding unexpected events, e.g. quickly stopping a lane change that has already been initiated, after hearing the horn of a car in your blind spot or seeing something in your periphery.

There were no higher order effects found for the RTI (no meaningful findings, as discussed in the results section) RVP or OSPAT. The main effects for time that were found demonstrate improved performance at peak compared to baseline, which was apparent under both modafinil and placebo. This may be explained by practice effects on the day of testing due to complex tasks being completed. Whilst the hypothesized improvements were not found, it is important to note that modafinil did not cause a detriment to performance on any cognitive task.

Any improvements were typically in the range of η^2_p=0.00 to η^2_p=0.20 when compared to placebo effects; primarily small effects and therefore practically meaningful effects were not missed due to low power.

Modafinil and behavioural measures (simulated driving performance)

It was hypothesized that modafinil would improve performance on the STISIM driving simulator. This hypothesis was partially supported, with driving performance results suggesting that there were no deleterious effects of modafinil consumption on driving ability. This is in contrast to the many driving tasks that appear to be impaired after dexamphetamine ingestion, including overall driving performance, divided attention tasks, speed and lane deviation, slowing in reaction time and inducement of tunnel vision (Silber et al., 2005).

A significant time x condition interaction was found for standard deviation of lateral lane position (SDLP). Whilst no significant differences were found in follow up tests due to low power, effect size analysis revealed less deviation at modafinil peak compared to modafinil baseline; with an increase in deviation found for placebo from baseline to peak. SDLP quantifies vehicle control by identifying the extent to which the vehicle diverges from a straight path within the lane, in the literature it is also referred to as a measure of 'wigglyness' and 'weaving'(S. Verster, Pandi-Perumal, Ramaekers, & de Gier, 2009). Reduced lane deviation for modafinil was also found by Gurtman, Broadbear and Redman (2008) with a single 300mg dose, however it should be noted these participants were sleep deprived. It does not appear that simulated driving performance on modafinil has been examined on a healthy non-sleep deprived population before now.

SDLP is a variable that is highly sensitive to the effects of medication (S. Verster et al., 2009). Benzodiazepine and related hypnotic compounds, such as temezapam and zolpidem as well as alcohol have been associated with SDLP impairment and as such an increase in variability of lane position (Banks, Catcheside, Lack, Grunstein, & McEvoy, 2004; Mattila, Vanakoski, Kalska, & Seppala, 1998; Partinen, Hirvonen, Hublin, Halavaara, & Hiltunen, 2003). There does not seem to be previous research on the effect of dexamphetamine on SDLP. However with research showing methamphetamine increases weaving (Logan, 1996; Logan, Fligner, & Haddix, 1998) and if performance on SSRT can indeed be used to predict SDLP (Jongen et al., 2011) (which the current study adds support), it may be hypothesized that dexamphetamine would increase variability of lane position.

This measure of lateral lane position is extremely sensitive to the effects of medications and illicit drugs; as variability increases, the control one has of the vehicle decreases and the risk of collisions increases(J. Verster et al., 2008). It would appear that modafinil enhances one's ability to drive safely through decreasing 'weaving' and subsequently decreasing the risk of collisions and serious injury.

A trend towards a significant time x condition interaction was apparent for number of centre line crossings. Further examination using partial eta squared revealed a large effect size between modafinil baseline and modafinil peak with fewer centre line crossings made at peak; no effect existed for the placebo condition. This measure has not been applied to modafinil previously and therefore comparing results is not possible. However it may be related to SDLP, as less variability in the lane would decrease the chances of crossing the centre line. Researchers have shown that drifting out of the lane is a typical behaviour exhibited by individuals who have taken methamphetamine (a more potent amphetamine compared to dexamphetamine)

and therefore may be found to a lesser degree with dexamphetamine. This finding suggests that in real world driving, individuals who had taken modafinil would appear to cross the centre line into the other lane on fewer occasions, decreasing the chance of head on collisions.

Whilst there were no significant interactions found for the divided attention task, a medium effect size for reaction time for 'correct' divided attention responses was found between modafinil baseline and peak. Reaction time was faster at modafinil peak than at baseline, an effect that was not replicated during placebo dosing. For the remaining divided attention measures there were little meaningful differences, with performance similar for both conditions. These findings are important due to the fact that dexamphetamine has been shown to consistently impair performance on divided attention tasks (Mills et al., 2001; Silber et al., 2005). This effect of dexamphetamine has been attributed to 'tunnel vision' or perceptual narrowing caused by the drug (Mills et al., 2001). It would therefore appear based on the findings of the current study, that modafinil does not induce tunnel vision.

Modafinil and performance feedback (visual analogue scales)

Whilst numerous self-report measures were taken in regards to perceived performance and willingness to drive on the STISIM driving simulator, no meaningful findings were found.

Willingness to drive measures were collected in order to assess overconfidence effects, as previous research has found this to exist for modafinil (Baranski et al., 2004; Baranski & Pigeau, 1997; Gurtman et al., 2008) but not dexamphetamine (Gurtman et al., 2008). The current study assessed overconfidence

from pre- to post- drive at peak drug levels, in future studies it may be beneficial to assess the measure by comparing subjective performance with an overall objective measure of driving performance.

Methodological limitations

One limitation of the current study is that only males were tested. This was done intentionally for a number of valid reasons; to assess young males who are known to be more risky than females and are over represented in motor vehicle accidents, and because males have lower levels of depression and anxiety (Kaplan & Saddock, 2007), allowing the researchers to control for the effects such an underlying condition may have on performance and results. This design decision to restrict the study population to only males decreases the variance in the sample resulting in an increase in experimental power. However it causes complications in terms of generalisability of this study's results. Wong et al. (1999) demonstrated that age as well as gender effects modafinil clearance processes; with the clearance rate in males decreasing with age and young females clearing the drug at a faster rate than young males. It can therefore be questioned whether males and females metabolise the drug slightly differently and whether this would in fact influence peak plasma levels and performance on the drug.

Another methodological issue to be considered is the amount of food consumed by each participant. Food intake and therefore modafinil absorption rate was controlled by asking participants to consume lunch in the three hour break between baseline and peak testing. Whilst this was kept consistent for all participants, the type of food and how much consumed was not. Participants were

asked not to consume any caffeinated products to control for the effect caffeine may have on performance. Due to the fact that the current study aimed to examine the effect of modafinil on real world tasks/real world experience (e.g. simulated driving ability), fasting would not have been appropriate. However future studies may wish to include a fasting period, or alternatively control the amount and type of food participants consume during the testing sessions.

The relatively small sample size must also be considered. Whilst main effects and interactions were found, a number of trends towards significance were also identified and examined by looking at effect sizes. Due to time constraints the minimum number of participants needed for a within subjects design to identify a large magnitude effect (f=.04) were tested. However through examining partial eta squared values to determine effect sizes of differences, it us unlikely that any practically meaningful effects (partial eta square $\geq$.09 were missed due to low power; see tables 9, 11, 13, 15 and 17 for higher order effect sizes for cognitive and behavioural measures.

The most important limitation of the current study is the fact blood plasma levels were not taken in order to determine peak plasma levels and thus ideal post drug testing time; as this may vary across participants. This was done to minimise the invasiveness of the testing procedure on participants. Peak drug testing was completed at 3 hours post drug administration, in accordance to similar studies (Wong et al., 1999). However this may be a methodological aspect for future researchers to consider.

Directions for future research

The current study aimed to examine modafinil on measures that had been shown to be negatively affected by dexamphetamine, based on previous research. It would be beneficial to complete the methodology used in the current study using 10mg dexamphetamine, as this is standard dosing in narcolepsy disorder (MIMS, 2009, 2009a), previous research has used this dosage to compare drug effects (William et al., 2008; Wong et al., 1999). This would enable a more valid comparison of any effects of modafinil and dexamphetamine. It would also be recommended that any future research uses blood plasma to identify peak plasma levels for a more reliable estimation of peak performance.

Summary and conclusions

In summary, the aim of the current study was to assess acute driving-related cognitive skills and simulated driving performance following a 200mg single dose of modafinil, using measures of driving performance that had been demonstrated to be negatively affected by dexamphetamine. The findings suggest that there were no deleterious effects of modafinil consumption on driving, a contrast to the robustly replicated deficits shown by dexamphetamine on comparable tasks. There is some indication of improved consistency of performance, with an increased ability to inhibit pre-potent responses and a reduction in lateral lane deviation and centre line crossings on modafinil. These findings, along with a subjective increase in alertness leads to the expectation of safer real world driving when compared to both placebo and dexamphetamine.

In conclusion, the findings of the current study indicate that modafinil selectively improves neuropsychological task performance in a functionally different

way compared to conventional stimulants, specifically dexamphetamine. The resulting differences in cognitive and behavioural performance may be attributable to the differing neurochemical profile of these drugs.

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Appendix A: Ethical Requirements

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Appendix A1: Information sheet

INFORMATION SHEET

The Effect of Modafinil on Simulated Driving Performance

Chief Investigator: Dr Raimondo Bruno

Researcher: Jessica Hartley*

**This research is being conducted as part of a Masters degree in the School of Psychology, UTAS.*

We would like to invite you to participate in a study aiming to better understand the way that the prescription drug modafinil effects aspects of driving related skills and simulated driving performance. The use of this drug is increasing Australia wide, and we are interested in better understanding its effects. There have been a number of studies which have shown some effects of stimulant drugs on driving related tasks but very few studies have examined modafinil. Getting a better understanding about modafinil is particularly important, not just to understand how the drug affects cognition, but also to be able to provide information for doctors to give to potential users of the drug.

Why have I been invited to participate in this research?

You are invited to take part in the study if you are male and aged 20-24 years old. In order for the results of the study to be clear, all participants need to speak English fluently, and have had no previous neurological or mental health problems. In addition participants must NOT use illicit drugs, smoke cigarettes daily or consume alcohol at harmful levels.

What will my participation involve?

Participating in this study is unlikely to cause any discomfort or distress. Firstly, if you are interested in taking part in the study, you will be invited to complete a series of confidential screening questionnaires. These will enquire about what your mood has been like recently. This will include a psychological distress scale, schizotypal personality questionnaire, a psychosis screener and some questions regarding your alcohol and drug use. All data collected will be kept in the strictest confidence, and the way we maintain this is described below. This screening process is simply to ensure that participants in the study are not taking medications or experiencing other issues that may cause a negative response to modafinil.

During the study, we will ask for some basic information about yourself (such as age, sex, years of schooling). There are a number of different short tasks investigating driving related skills as well as completing a driving scenario on a state-of-the-art driving simulator. Previous studies using the same dose of modafinil have found side effects for some participants, including dry mouth, mild headaches and mild nausea. There will be two testing sessions which will occur at the University of Tasmania, and will take around four hours each. You will be reimbursed $80 for your time and out-of-pocket expenses.

Before taking part in the study you must organise for a reliable friend or family member to collect you from the lab at the end of the testing session, in case you are still experiencing any effects following the possible administration of modafinil. The researcher will check that this has been organised before the testing session begins. When the nominated person collects you, they will be given a copy of the medication information sheet about modafinil, and the main points will be verbally explained. Namely, it will be explained that they should ensure you do not drive a vehicle or operate machinery for the rest of the day, and do not consume alcohol. In the unlikely event that you do experience unpleasant side effects while completing the testing, the researchers are trained in first aid, and a registered nurse will be available on site to provide further assistance if required. Additionally, the researcher will explain that in the unlikely event of you experiencing an adverse reaction once you have left the premises, you should contact your doctor or be taken to hospital immediately.

How private is the information that I give?

It is important for you to know that all data collected will be kept in the strictest confidence. All data will be identified by a coding system and no names or contact numbers will appear on any records. In this way, your identity is protected, and there will be no risk of legal or social problems arising from your participating in the study. All information gathered in the study will be reported as grouped data, and because no personal information is recorded, no individual participants will be identifiable in the research output. Data from the study will be stored securely for five years in locked cabinets in the School of Psychology, as is legally required, and then destroyed by shredding. It should be noted that screening tests of those participants who do not meet the inclusion criteria for the study will be destroyed immediately.

Can I withdraw from the research if I wish?

Participation in this study is entirely voluntary. You may, at any time, decline to answer any question you so wish, or withdraw from the study without effect or explanation. You will be given a copy of this information sheet to keep. Please retain this information sheet in case you decide at a later data that you would like to retract your data from the study.

Who do I need to contact if I have any questions about the research?

If you would like more information about the research, please contact Dr Raimondo Bruno at the School of Psychology, UTAS, on 6226 2190 or Raimondo.Bruno@utas.edu.au. If you would like to find out about the results of the study, these will be available from Dr Bruno after November 2011 or at www.utas.edu.au/psychol.

Has this research been approved by an ethics committee?

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H11386.

Who can I contact if I have any concerns?

If you have any personal concerns related to the study, you may choose to discuss these concerns confidentially with a counsellor at the University Psychology Clinic free of charge. Confidential appointments may be made on (03) 6226 2805.

Thank you for your interest in the study and for taking the time to read this information sheet. We hope you will be interested in participating in this study.

Raimondo Bruno
Chief Investigator
(03) 6226 2190

Jessica Hartley
Student Researcher

Appendix A2: Consent form

The Effect of Modafinil on Simulated Driving Performance

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1. I have read and understood the 'Information Sheet' for this study.
2. I have read and understood the 'Consumer Medicine Information' regarding modafinil.
3. The nature and possible effects of the study have been explained to me.
4. I understand that the study involves:
   - Attending two testing sessions of approximately four hour's duration
   - Completing a series of cognitive driving related tasks and completing a driving scenario on a driving simulator
   - Completing a series of mental health tests
5. I understand that all research data will be securely stored on the University of Tasmania premises for five years, and will then be destroyed.
6. Any questions that I have asked have been answered to my satisfaction.
7. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.
8. I understand that the researchers will maintain my identity confidential and that any information I supply to the researcher(s) will be used only for the purposes of the research.
9. I agree to participate in this investigation and understand that I may withdraw at any time without any effect, and if I so may request that any data I have supplied to date be withdrawn from the research.
10. This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H11386.

Name of Participant:

Signature: Date:

Statement by Investigator

☐ I have explained the project & the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation

Name of investigator

Signature of investigator Date

Appendix A3: Modafinil consumer medical information

MODAVIGIL®

Modafinil

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about MODAVIGIL® tablets. As this leaflet does not contain all the available information, it is important that you talk to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you receiving MODAVIGIL® against the benefits this medicine is expected to have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet. You may need to read it again.

What MODAVIGIL® is used for

MODAVIGIL® is used to improve wakefulness in people with excessive daytime sleepiness associated with the medical condition known as narcolepsy or with Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS), or shift work sleep disorder (SWSD).

In narcolepsy, there is a sudden and irresistible tendency to fall asleep during normal waking hours. This happens at unpredictable times, even when it is inappropriate or may be unsafe to do so. MODAVIGIL® decreases this unwanted excessive daytime sleepiness.

With OSAHS, daytime sleepiness may occur due to an interrupted night time sleep. MODAVIGIL® only treats the symptom of sleepiness and does not treat the cause of OSAHS. Whilst taking MODAVIGIL® you should continue with treatments intended to help manage your underlying medical condition, such as Continuous Positive Airway Pressure, unless your doctor tells you otherwise.

MODAVIGIL® may also help to keep you awake during your working shift if you have been diagnosed with moderate to severe chronic Shift Work Sleep Disorder (SWSD).

Precisely how MODAVIGIL® works is not known, but it is known that it acts on the central nervous system (the brain). It differs from other stimulant medicines that promote wakefulness. MODAVIGIL® increases wakefulness. Unlike other stimulants it does not overstimulate or produce a "high" feeling.

Your doctor may have prescribed MODAVIGIL® for another reason. Ask you doctor if you have any questions about why MODAVIGIL® has been prescribed for you.

Before you take MODAViGIL®

When you must not take it

You must not take MODAVIGIL® if you:

- are allergic to modafinil or any of the other ingredients listed at the end of this leaflet. (See "MODAVIGIL® tablets description"). Signs of allergic reaction may include a skin rash, itching, shortness of breath or swelling of the face, lips or tongue
- are pregnant, or likely to become pregnant.

Do not take MODAVIGIL® if the packaging is torn or shows signs of tampering or the tablets do not look quite right.

Do not take MODAVIGIL® if the expiry date on the pack has passed.

If you are not sure about whether you should start taking MODAVIGIL®, you should contact your doctor.

Before you take it

Before you start taking MODAVIGIL® you should discuss with your doctor any of the following points which apply to you. If you:

- are under 18 or over 65 years old
- have a history of mental health problems
- have heart problems, including, for example, angina (chest pain), previous heart attack, enlarged heart
- have an abnormal/irregular heart rhythm
- have high blood pressure or your high blood pressure is controlled by medication

- have kidney or liver problems
- are taking hormonal contraceptives
- could become pregnant
- are currently receiving treatment for anxiety
- are breastfeeding
- are taking brain stimulants, such as methylphenidate
- are taking any medicines to treat depression, including those called monoamine oxidase inhibitors (MAOIs)
- are taking medicines to treat epilepsy or fits, such as phenytoin, carbamazepine and phenobarbitone
- are taking medicines to treat fungal infections, such as ketoconazole and itraconazole
- are taking medicines to help you sleep (sedatives)
- are taking rifampicin, an antibiotic used to treat tuberculosis
- are taking cyclosporin, a medicine used to stop organ transplant rejection
- are taking propranolol, a medicine used to treat, for example, high blood pressure, heart problems or migraine
- are taking warfarin, a medicine used to prevent unwanted blood clotting
- are taking theophylline, a medicine used in asthma and lung problems
- are taking any other medicines, including any available without a prescription from your pharmacy, supermarket or health food shop

Tell your doctor about any of the above before you take MODAVIGIL®. Your doctor will discuss the risks and benefits of using MODAVIGIL®.

How to take MODAVIGIL®

It is important that you take this medicine as directed by the doctor. Your doctor will tell you how much you should take, when and how often. Follow your doctor's instructions. If you are unsure ask your doctor or pharmacist.

How much should you take

Each MODAVIGIL® tablet contains 100mg of modafinil.

The usual daily dose of modafinil depends on individual response. For sleepiness associated with narcolepsy or OSAHS, the dose ranges from 200mg to 400mg.

Each day you should take either:

- two MODAVIGIL® tablets

  or

- up to four MODAVIGIL® tablets.

For SWSD, a dose of 200mg is recommended.

Do not exceed the recommended daily dose unless directed to do so by your doctor.

When and how should you take the tablets

For sleepiness associated with narcolepsy or OSAHS, you should take your MODAVIGIL® tablets either:

- as two separate doses, one in the morning and one at midday,

  or

- as one dose, in the morning.

For narcolepsy or OSAHS, do not take your MODAVIGIL® tablets later than midday, or you may have trouble sleeping at night.

For SWSD, you should take your MODAVIGIL® tablets as a single dose 1 hour prior to commencing your shift work.

Swallow the tablets whole with a little water.

NOTE: Your doctor may start your treatment with less than two tablets a day.

If you need more than two tablets per day, your doctor should increase the dose stepwise, one additional tablet at a time, depending on how you respond to the treatment. The highest dose is four tablets per day.

If you are currently on another treatment for narcolepsy, your doctor will advise you how best to withdraw from that treatment and begin taking MODAVIGIL®. Other stimulants used for narcolepsy may cause a "high" feeling. Be aware therefore that you may feel different as you withdraw from other stimulants. MODAVIGIL® is not associated with this "high" feeling. It works on excessive daytime sleepiness.

MODAVIGIL® only treats the symptom of sleepiness. Other treatments intended to help manage your underlying medical condition

should still be used regularly, unless your doctor tells you otherwise. You should commence or continue disease-modifying interventions (for example, Continuous Positive Airway Pressure).

REMEMBER: This medicine is only for you. Only a doctor can prescribe it for you. Never give it to anyone else. It may harm them, even if their symptoms appear to be the same as yours.

If you forget to take it

If you miss a dose of MODAVIGIL® tablets, just take the next dose at your usual time. Do not take an extra dose to "catch up".

While you are taking MODAVIGIL®

Things you must do

If you become pregnant while you are taking MODAVIGIL®, stop taking it and tell your doctor immediately.

If you are about to be started on any new medicine, tell your doctor and pharmacist that you are taking MODAVIGIL®.

Tell your doctor if you believe that MODAVIGIL® is not helping your condition. Your doctor may need to change the dose.

Things you must not do

Do not give MODAVIGIL® to anyone else, even if they have the same symptoms as you.

Things to be careful of

MODAVIGIL® may reduce the effectiveness of oral contraceptives. If you are using these forms of contraceptives while taking MODAVIGIL® (and for 1 month after you stop treatment with MODAVIGIL®) you should either use: an alternative birth control method or another effective birth control method together with your current contraceptive.

Do not drive or operate machinery until you know how MODAVIGIL® affects you.

Side Effects

MODAVIGIL® may cause you to have a serious rash.

Stop MODAVIGIL® and call your doctor right away or get emergency treatment if you have a skin rash, hives, sores in your mouth, or your skin blisters and peels, or if you have any sudden wheeziness, difficulty in breathing, swelling, rash or itching (especially affecting the whole body).

MODAVIGIL® may cause the following side effects in some people. In clinical studies, these side effects also occurred in people who received non-active (sugar) tablets. Tell your doctor if you notice any of these:

- headache
- nausea
- diarrhoea
- dry mouth
- poor appetite
- runny nose
- sore throat
- nervous feeling
- dizziness.

Tell your doctor immediately if any of the following occur:

- mental (psychiatric) symptoms. Symptoms include depression, anxiety, hallucinations, mania, thoughts of suicide or other mental problems.

Other side effects not listed above may also occur in some patients. Tell your doctor if you notice anything that makes you feel unwell. Do not be alarmed by this list of possible side effects. You may not experience any of them.

Overdosage

Immediately telephone your doctor, or the Poisons Information Centre (telephone 13 11 26 in Australia or 0800 764 766 in New Zealand), or go to the emergency department of your nearest hospital, if you think you or anyone else may have taken too much MODAVIGIL®. Do this, even if there are no signs of discomfort or poisoning.

MODAVIGIL® tablets description

Each MODAVIGIL® tablet contains 100mg of modafinil.

Each tablet also contains the following inactive ingredients:

- lactose
- starch-maize
- magnesium silicate dihydrate
- sodium croscarmellose
- povidone
- purified talc
- magnesium stearate.

MODAVIGIL® tablets are white, round-shaped with smooth convex sides.

Each pack contains either 10, 30 or 60 tablets.

Storage

Keep MODAVIGIL® tablets in the original pack until it is time to take them.

Store MODAVIGIL® tablets below 25 degrees C. Keep the pack in a cool, dry place and away from direct heat and sunlight.

Do not store MODAVIGIL® tablets in the bathroom or near a sink.

Keep MODAVIGIL® tablets where children cannot reach them. A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

The Australian Registration Number is AUST R 82350.

This is not all the information available on MODAVIGIL®. If you have any more questions or are unsure about anything, ask your doctor or pharmacist.

MODAVIGIL® is supplied in Australia by:
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AUSTRALIA

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Appendix B: Testing Materials

Appendix B1: Screening questionnaire

Appendix B2: Profile of Mood States-Short Form

Appendix B3: Karolinska Sleepiness Scale

Appendix B4: Visual analogue scale pre test

Appendix B5: Visual analogue scale post test

Appendix B6: Visual analogue scale drug effects

Appendix B1: Screening Questionnaire

Screening questionnaire

How old are you? _____

Participants must be males between 20 and 24.

Do you have a full drivers licence? How many years have you been driving for? _____

Participants must have at least 3 years of regular driving experience

Do you smoke? Yes ☐ No ☐

If yes, participant is not eligible for the study.

Have you ever used any of the following:

Heroin	Yes ☐	No ☐
Methamphetamine (speed powder, base, ice)	Yes ☐	No ☐
Ecstasy	Yes ☐	No ☐
Cocaine	Yes ☐	No ☐
Hallucinogens (e.g. LSD, acid, magic mushrooms)	Yes ☐	No ☐
Inhalants (e.g. amyl nitrate, rush, glue, laughing gas, petrol, paint)	Yes ☐	No ☐
Cannabis	Yes ☐	No ☐

Have you ever used pharmaceutical medications without them being prescribed to you, e.g. morphine, methadone, oxycodone, pharmaceutical stimulants, antipsychotics, antidepressants? Yes ☐ No ☐

How recently have you used any of the above? _____

At your peak, how often did you use any of the above? _____

*If participant demonstrates **recent and/or history of regular use** (i.e. more than once a month ever, and within the last 12 months) they are **not** eligible for the study.*

Do you have a history of any of the following:

Major Anxiety/Depression	Yes ☐	No ☐
Mania	Yes ☐	No ☐
Psychosis/ any other psychological illness	Yes ☐	No ☐
Attention deficit/hyperactivity disorder	Yes ☐	No ☐
Alcohol or substance use problems	Yes ☐	No ☐
Hypertension	Yes ☐	No ☐
Cardiac problems (inc. chest pain/angina)	Yes ☐	No ☐
Liver impairment	Yes ☐	No ☐
Kidney impairment	Yes ☐	No ☐
Epilepsy	Yes ☐	No ☐
Chronic Pain	Yes ☐	No ☐
Asthma	Yes ☐	No ☐
Skin complaints	Yes ☐	No ☐

*If **yes** to any of the above, the participant is **not** eligible for the study.*

Are you currently taking any medications: (including over-the-counter medications)	Yes ☐	No ☐

For safety, please verify specifically:

Methylphenidate (a drug used for ADHD & narcolepsy)	Yes ☐	No ☐
Triazolam (or any benzodiazepine used, for example, in the treatment of insomnia or anxiety)	Yes ☐	No ☐
Psychiatric meds for depression (inc. Herbal- hypericum St.Johns Wort), or schizophrenia	Yes ☐	No ☐
Phenytoin or other anticonvulsants (any drugs used for epilepsy)	Yes ☐	No ☐
Warfarin (anticoagulant, blood thinner)	Yes ☐	No ☐
Codeine, fentanyl (or any drugs used for chronic pain)	Yes ☐	No ☐
Hormone supplements (testosterone)	Yes ☐	No ☐
Daily paracetamol or ibuprophen	Yes ☐	No ☐
Medications to treat fungal infections	Yes ☐	No ☐
Medications to help you sleep	Yes ☐	No ☐
Any other medicines, including any available without a prescription from a pharmacy, supermarket or health food store	Yes ☐	No ☐
Any medications over the past week (other than PRN paracetamol)	Yes ☐	No ☐

*if **yes** to any of the above, the participant is **not** eligible for the study.*

AUDIT

These questions are related to your use of alcohol. Remember, any information you provide is completely confidential.

Please circle the most appropriate response

Q1. How often do you have a drink containing alcohol?							
0	Never	**1**	Monthly or less	**2**	2-4 times a month	**3**	2-3 times a week	**4**	4 or more times a week
Q2. How many drinks containing alcohol do you have on a typical day when you are drinking?							
0	1 or 2	**1**	3 or 4	**2**	5 or 6	**3**	7 to 9	**4**	10 or more
Q3. How often do you have six or more drinks on one occasion?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q4. How often during the last year have you found that you were not able to stop drinking once you had started?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q5. How often during the last year have you failed to do what was normally expected from you because of drinking?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q6. How often during the last year have you needed a first drink in the morning to get yourself going, after a heavy drinking session?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q7. How often during the last year have you had a feeling of guilt or remorse after drinking?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?							
0	Never	**1**	Less than monthly	**2**	Monthly	**3**	Weekly	**4**	Daily or almost daily
Q9. Have you or someone else been injured as a result of your drinking?							

0	No	**2**	Yes, but not in last year	**4**	Yes, during the last year

Q10. Has a relative or friend or doctor or other health worker been concerned about your drinking or suggested you cut down?

0	No	**2**	Yes , but not in last year	**4**	Yes, during the last year

Total= (>19)

These questions are related to how you have been feeling over the last 4 weeks. Remember, any information you provide is completely confidential.

Please circle the most appropriate response.

In the last 4 weeks, about how often –

1. Did you feel tired out for no good reason?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

2. Did you feel nervous?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

Note: If response 1 chosen, go to Q4

3. Did you feel so nervous that nothing could calm you down?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

4. Did you feel hopeless?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

5. Did you feel restless or fidgety?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

Note: If response 1 chosen, go to Q7

6. Did you feel so restless that you could not sit still?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

7. Did you feel depressed?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

8. Did you feel that everything was an effort?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

9. Did you feel so sad that nothing could cheer you up?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

10. Did you feel worthless?

All of the time	5
Most of the time	4
Some of the time	3
A little of the time	2
None of the time	1

Total=

(≥30)

Psychosis Screener

1. In the past 12 months, have you felt that your thoughts were being directly interfered with or controlled by another person?	Yes ☐ No ☐
1a. Did it come about in a way that any people would find hard to believe, for instance, through telepathy?	Yes ☐ No ☐
2. In the past 12 months, have you had a feeling that people were too interested in you?	Yes ☐ No ☐
2a. In the past 12 months, have you had a feeling that things were arranged so as to have a special meaning for you, or even that harm might come to you?	Yes ☐ No ☐
3. Do you have any special powers that most people lack?	Yes ☐ No ☐
3a. Do you belong to a group of people who also have these special powers?	Yes ☐ No ☐
4. Has a doctor ever told you that you may have schizophrenia?	Yes ☐ No ☐

Total=

(≥1)

SPQ

Please answer each item by checking Y (Yes) or N (No). Answer ***all*** items even if unsure of your answer. When you have finished, check over each one to make sure you have answered them.

1. People sometimes find me aloof and distant	Yes ☐	No ☐
2. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?	Yes ☐	No ☐
3. People sometimes comment on my unusual mannerisms and habits	Yes ☐	No ☐
4. Are you sometimes sure that other people can tell what you are thinking?	Yes ☐	No ☐
5. Have you ever noticed a common event or object that seemed to be a special sign for you?	Yes ☐	No ☐
6. Some people think that I am a very bizarre person	Yes ☐	No ☐
7. I feel I have to be on my guard with friends	Yes ☐	No ☐
8. Some people find me a bit vague and elusive during a conversation	Yes ☐	No ☐
9. Do you often pick up hidden threats or put downs from what people say or do?	Yes ☐	No ☐
10. When shopping do you get the feeling that other people are taking notice of you?	Yes ☐	No ☐
11. I feel very uncomfortable in social situations involving unfamiliar people	Yes ☐	No ☐
12. Have you had experiences with astrology, seeing the future, UFos, ESP, or a sixth sense?	Yes ☐	No ☐
13. I sometimes use words in unusual ways	Yes ☐	No ☐
14. Have you found that it is best not to let other people know too much about you?	Yes ☐	No ☐
15. I tend to keep in the background on social occasions	Yes ☐	No ☐
16. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?	Yes ☐	No ☐
17. Do you often have to keep an eye out to stop people from taking advantage of you?	Yes ☐	No ☐
18. Do you feel that you are unable to get 'close' to people?	Yes ☐	No ☐
19. I am an odd, unusual person	Yes ☐	No ☐

20. I find it hard to communicate clearly what I want to say to people	Yes ☐	No ☐
21. I feel very uneasy talking to people I do not know well	Yes ☐	No ☐
22. I tend to keep my feeling to myself	Yes ☐	No ☐

Total=

(≥17)

Appendix B2: Profile of Mood States-Short Form

Participant Code:

Test Point:

PROFILE OF MOOD STATES-SHORT FORM

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle ONE answer to the right, which best describes how you are feeling AT THE MOMENT.

The numbers refer to these phrases:
0=not at all
1=a little
2=moderately
3=quite a bit
4= extremely

1. Tense.....0 1 2 3 4
2. Angry.....0 1 2 3 4
3. Worn out.....0 1 2 3 4
4. Unhappy.....0 1 2 3 4
5. Lively.....0 1 2 3 4
6. Confused.....0 1 2 3 4
7. Peeved.....0 1 2 3 4
8. Sad.....0 1 2 3 4
9. Active.....0 1 2 3 4
10. On Edge.....0 1 2 3 4
11. Grouchy.....0 1 2 3 4
12. Blue.....0 1 2 3 4
13. Energetic..... 0 1 2 3 4
14. Hopeless.....0 1 2 3 4
15. Uneasy.....0 1 2 3 4
16. Restless.....0 1 2 3 4
17. Unable to Concentrate.....0 1 2 3 4
18. Fatigued.....0 1 2 3 4
19. Annoyed.....0 1 2 3 4
20. Discouraged.....0 1 2 3 4
21. Resentful.....0 1 2 3 4
22. Nervous.....0 1 2 3 4
23. Miserable.....0 1 2 3 4
24. Cheerful.....0 1 2 3 4
25. Bitter.....0 1 2 3 4
26. Exhausted.....0 1 2 3 4
27. Anxious.....0 1 2 3 4
28. Helpless.....0 1 2 3 4
29. Weary.....0 1 2 3 4
30. Bewildered.....0 1 2 3 4
31. Furious.....0 1 2 3 4
32. Full of pep.....0 1 2 3 4
33. Worthless.....0 1 2 3 4
34. Forgetful.....0 1 2 3 4
35. Vigorous.....0 1 2 3 4
36. Uncertain about things.....0 1 2 3 4
37. Bushed.....0 1 2 3 4

Appendix B3: Karolinska Sleepiness Scale

Sleepiness Scale

Please circle on the following scale of 1 to 9 how you feel AT THE PRESENT MOMENT:

1. Very alert
2.
3. Alert – normal level
4.
5. Neither alert nor sleepy
6.
7. Sleepy – but no effort to stay awake
8.
9. Very sleepy, great effort to stay awake, fighting

Appendix B4: Visual analogue scale pre test

PRE TEST **Participant number:** **Test point:**

Visual Analogue Scales of Subjective Performance

Please mark on each line at the point which most accurately reflects your level of agreeness AT THE MOMENT with the below statement:

1. I feel alert

STRONGLY AGREE ——————————— STRONGLY DISAGREE

2. I feel that I will be able to perform the driving tasks to the best of my ability

STRONGLY AGREE ——————————— STRONGLY DISAGREE

3.I do not feel that my driving would be impaired right now

STRONGLY AGREE ——————————— STRONGLY DISAGREE

4.I feel capable of driving safely right now

STRONGLY AGREE ——————————— STRONGLY DISAGREE

5.I am confident in my abilities to drive the simulator right now

STRONGLY AGREE ——————————— STRONGLY DISAGREE

6.I am confident in my abilities to obey all road rules

STRONGLY AGREE ——————————— STRONGLY DISAGREE

Appendix B5: Visual analogue scale post test

POST TEST Participant number: Test point:

Visual Analogue Scales of Subjective Performance

Please mark on each line at the point which most accurately reflects your level of agreeness AT THE MOMENT with the below statement:

1. I feel alert

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

2. I feel that I was able to perform the driving tasks to the best of my ability

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

3. I do not feel that my driving was impaired

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

4. I feel confident that I drove safely

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

5. I am confident in my abilities to drive the simulator

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

6. I am confident that I obeyed the road rules

STRONGLY AGREE ——————————————— STRONGLY DISAGREE

Appendix B6: Visual analogue scale drug effects

Participant number: Test point:

Visual Analogue Scales of Subjective Drug Effects

Please mark on each line at the point which most accurately reflects your level of agreeness AT THE MOMENT with the below statement:

1. Strength of drug effect

NO EFFECT ——————————————— VERY STRONG EFFECT

2. Liking of the drug effect

DISLIKE VERY MUCH ——————————————— LIKE VERY MUCH

3. Alert level

NOT ALERT ——————————————— VERY ALERT

4. Intoxication

NOT INTOXICATED ——————————————— VERY INTOXICATED

Do you think you ingested modafinil or placebo today?

_____